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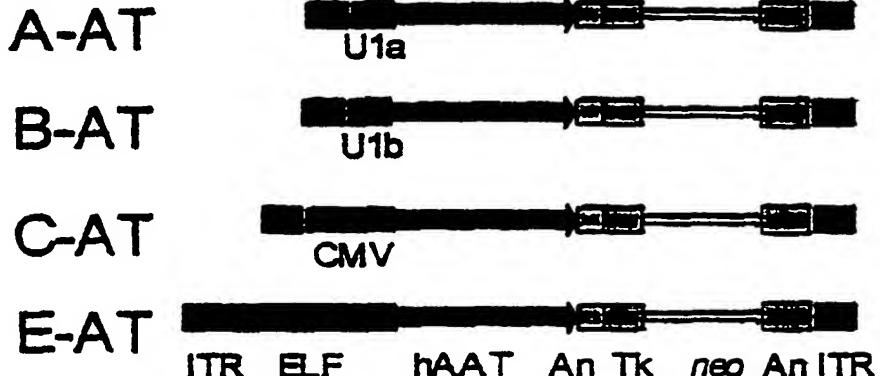


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(54) Title: MATERIALS AND METHODS FOR GENE THERAPY



(57) Abstract

The subject invention concerns materials and methods for gene therapy. One aspect of the invention pertains to vectors which can be used to effect genetic therapy in animals or humans having genetic disorders where expression of high levels of a protein of interest are required to treat or correct the disorder. The subject invention also pertains to methods for treating animals or humans in need of gene therapy to treat or correct a genetic disorder. The materials and methods of the invention can be used to provide therapeutically effective levels of a protein that is non-functional, or that is absent or deficient in the animal or human to be treated. In one embodiment, the materials and methods can be used to treat alpha-1-antitrypsin deficiency.

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DESCRIPTIONMATERIALS AND METHODS FOR GENE THERAPY

5       The subject invention was made with government support under a research project supported by National Institute of Health NHLBI Grant No. HL 59412. The government has certain rights in this invention.

Cross-Reference to a Related Application

10      This application claims priority from provisional application U.S. Serial No. 60/083,025, filed April 24, 1998.

Background of the Invention

15      Alpha-1-antitrypsin (AAT) deficiency is the second most common monogenic lung disease in man, accounting for approximately 3% of all early deaths due to obstructive pulmonary disease. AAT protein is normally produced in the liver, secreted into the serum and circulated to the lung where it protects the fine supporting network of elastin fibers from degradation by neutrophil elastase. Current therapy for AAT deficiency includes avoidance of cigarette smoke exposure and weekly intravenous infusions of recombinant human AAT (hAAT) protein. Attempts to devise gene therapy strategies to replace AAT either in the lung itself or within any of a number of other tissues which are capable of AAT secretion have been limited by the short duration of expression from some vectors and by the relatively high circulating levels of AAT which is required for therapeutic effect. Methods of gene therapy have been described in U.S. Patent No. 5,399,346.

20      It has recently been demonstrated that adeno-associated virus (AAV) vectors are capable of stable *in vivo* expression and may be less immunogenic than other viral vectors (Flotte *et al.*, 1996; Xiao *et al.*, 1996; Kessler *et al.*, 1996; Jooss *et al.*, 1998). AAV is a non-pathogenic human parvovirus whose life cycle naturally includes a mechanism for long-term latency. In the case of wild-type AAV (wtAAV), this persistence is due to site-specific integration into a site on human chromosome 19 (the AAVSI site) in the majority of cells (Kotin *et al.*, 1990), whereas with recombinant

AAV (rAAV) vectors, persistence appears to be due to a combination of episomal persistence and integration into non-chromosome 19 locations (Afione *et al.*, 1996; Kearns *et al.*, 1996). Recombinant AAV latency also differs from that of wtAAV in that wtAAV is rapidly converted to double-stranded DNA in the absence of helper virus (*e.g.*, adenovirus) infection, while with rAAV leading strand synthesis is delayed in the absence of helper virus (Fisher *et al.*, 1996; Ferrari *et al.*, 1996). U.S. Patent No. 5,658,785 describes adeno-associated virus vectors and methods for gene transfer to cells.

Kessler *et al.* (1996) demonstrated that murine skeletal myofibers transduced by an rAAV vector were capable of sustained secretion of biologically active human erythropoietin (hEpo), apparently without eliciting a significant immune response against the secreted hEpo. See also U.S. Patent No. 5,858,351 issued to Podskakoff *et al.* Likewise, Murphy *et al.* (1997) have observed the expression and secretion of sustained levels of leptin in *ob/ob* mice after AAV muscle transduction. Brantly *et al.* (U.S. Patent No. 5,439,824) disclose methods for increasing expression of AAT using vectors comprising intron II of the human AAT gene. However, the level of leptin expression observed was only in the range of 2 to 5 ng/ml. Therapy for AAT deficiency requires serum levels of at least about 800  $\mu$ g/ml. Thus, there remains a need in the art for a means of providing therapeutically beneficial levels of a protein to a person in need of such treatment.

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#### Brief Summary of the Invention

The subject invention concerns materials and methods for gene therapy. One aspect of the invention pertains to vectors which can be used to provide genetic therapy in animals or humans having a genetic disorder where relatively high levels of expression of a protein is required to treat the disorder. The vectors of the invention are based on adeno-associated virus (AAV). The vectors are designed to provide high levels of expression of heterologous DNA contained in the vector. In one embodiment, the vectors comprise AAV inverted terminal repeat sequences and constitutive or regulatable promoters for driving high levels of gene expression. The subject invention also pertains to methods for treating animals or humans in need of gene therapy, *e.g.*, to correct a genetic deficiency disorder.

Brief Description of the Drawings

Figure 1 shows rAAV-AAT vector cassettes used according to the subject invention. The A-AT and B-AT constructs contain the promoters from the small nuclear RNA genes, U1a and U1b, respectively. The C-AT construct contains the CMV promoter, whereas the E-AT vector uses the human elongation factor 1- $\alpha$  (ELF in the figure) promoter. ITR refers to AAV inverted terminal repeat; An refers to polyA signal; Tk refers to the HSV thymidine kinase promoter; neo refers to the Tn5 neomycin phosphotransferase gene.

Figure 2 shows hAAT secretion rates *in vitro* from transiently transfected murine C2C12 myoblast cell line using expression vectors according to the subject invention. C-AT does not differ significantly from E-AT, but both differ from A-AT and B-AT ( $p<0.05$ ) AAT expression was detected using an ELISA assay specific for human AAT.

Figure 3 shows hAAT secretion rates *in vitro* from stably transduced murine C2C12 myoblast cell line using viral particles comprising expression vectors according to the subject invention. The mean rates of secretion from G418-resistant cultures 1 mo after transduction with either packaged E-AT vector or packaged C-AT vector are shown. In each instance, a "low" multiplicity transduction ( $4 \times 10^5$  particles/cell) and a high multiplicity transduction ( $4 \times 10^6$  particles/cell) were performed. E-AT "low" and "high" are greater than "high" multiplicity C-AT ( $P=0.02$ ) but are not significantly different from each other ( $n=3$ ). AAT expression was detected using an ELISA assay specific for human AAT.

Figure 4 shows additional constructs tested for hAAT expression. The murine myoblast C2C12 cells were grown in 35-mm wells with approximately  $4 \times 10^5$  cell per well and were transfected with 5  $\mu$ g of the appropriate plasmid DNA using Superfect transfection (Qiagen Inc., CA). Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA. Each bar represents the mean of results from three experiments (triplicate in each experiment).

Data from transfection experiments indicate that the expression from p43CB-AT was at least three times higher than that from C-AT *in vitro*.

Figures 5A and 5B show sustained secretion of therapeutic levels of hAAT using either the C-AT vector or the E-AT vector in either SCID or C57BL mice. Figure 5A shows the mean total serum levels of hAAT observed in groups of either SCID (squares)

or C57BL (circles) mice receiving either low dose ( $5 \times 10^{11}$  particles) (open symbols) or high dose ( $1.4 \times 10^{13}$  particles) (filled symbols) single injections into muscle of the C-AT vector measured at time points ranging from 1 to 16 wk after injection. For each strain, the high-dose curve is significantly different from the low-dose curve ( $P=0.009$  for SCID,  $P=0.02$  for C57BL), but the strains do not differ from each other. Figure 5B shows analogous data with the E-AT vector. None of these differences were significant.

Figure 5C shows long term secretion of hAAT from murine muscle transduced with C-AT. C57B1/6 or C57B1/6-SCID mice received  $3.5 \times 10^{10}$  IU,  $1.4 \times 10^{13}$  particles/mouse. One year after injection, serum hAAT levels were still 400  $\mu\text{g}/\text{ml}$  in C57B1/6-SCID and 200  $\mu\text{g}/\text{ml}$  in C57B1/6. This level are comparable with the peak levels observed (800 or 400  $\mu\text{g}/\text{ml}$ , respectively).

Figure 6 shows an immunoblot of sera taken from several of the C-AT vector-treated mice at 11 weeks after vector administration. Ten microliters of a 1:100 dilution of serum was electrophoresed by 10% SDS/PAGE, blotted, and incubated with 1:1,500 dilution of goat anti-hAAT-horseradish peroxidase conjugate (Cappel/ICN). Samples from three high-dose SCID (h1-h3), one high-dose C57BL (h3), and three low-dose C57BL (l01-l03) were included, along with one negative control (saline-injected = sal) serum to indicate the level of reactivity with endogenous mAAT. As a standard, hAAT was added either to negative-control C57BL serum (first hAAT lane) or to PBS (second hAAT) lane to final equivalent serum concentration of 100  $\mu\text{g}/\text{ml}$ .

Figures 7A and 7B show that some BALB/c mice mount humoral immune responses to hAAT, which correlate with lower serum levels but no observable toxicity. Figure 7A shows serum hAAT levels and Figure 7B shows serum anti-hAAT antibody levels as determined by ELISA performed on serum taken from mice injected with  $1 \times 10^{11}$  particles of the C-AT vector. Each set of symbols represents an individual animal (□, no. 1; △, no. 2; ○, no. 3). Note the inverse correlation between the presence of antibody and the presence of circulating hAAT.

Figure 8 shows the persistence of rAAV-AAT vector DNA in high molecular weight form. PCR products were amplified from DNA prepared by Hirt extraction from three SCID mice injected 16 wk earlier with  $5 \times 10^{11}$  resistant-particles of C-AT and analyzed by Southern blot. The high molecular weight Hirt pellet (genomic DNA lanes) and the low molecular weight supernatant (episomal DNA lanes) were analyzed

separately. Control lanes include a sample in which an hAAT cDNA plasmid was the template DNA (+) and a control in which water was the template (-). In this internal PCR reaction, a 500-bp product is expected regardless of whether or not the vector genome is integrated.

5       **Figure 9** shows serum hAAT in C57B1/6 mice transduced with C-AT and p43CB-AT. C57B1/6 mice were injected in muscle with C-AT ( $3.5 \times 10^{10}$  IU/mouse,  $1 \times 10^{12}$  particles/mouse) or p43CB-AT ( $6 \times 10^9$  IU,  $1 \times 10^{12}$  particles/mouse). The level of hAAT from p43CB-AT were projected based on an estimation of the equivalent dosage (infectious unit) of C-AT.

10      **Figure 10** shows enhancement of CMV promoter activity by a synthetic enhancer in C2C12 cells. The murine myoblast C2C12 cells were grown in 35-mm wells with approximately  $4 \times 10^5$  cell per well and were transfected with  $5 \mu\text{g}$  of p.43rmsENC-AT vector DNA using SUPERFECT transfection (Qiagen Inc, CA). Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA. 15      Each bar represents the mean of results from one experiment (triplicate).

20      **Figure 11** shows secretion of hAAT from mouse liver cells (HO15) transfected with different constructs. The murine liver cells (HO15) were grown in 35-mm wells with approximately  $4 \times 10^5$  cell per well and were transfected with  $5 \mu\text{g}$  of the plasmid DNA using LIPOFECTAMINE reagents (Life Technologies Inc, MD). Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA. Each bar represents the mean of results from two experiments (triplicate).

25      **Figure 12** shows secretion of hAAT from mouse liver cells (HO15) transfected using different methods. The murine liver cells (HO15) were grown in 35-mm wells with approximately  $4 \times 10^5$  cell per well and were transfected with  $5 \mu\text{g}$  of the p43CB-AT vector using Superfect (Qiagen Inc., CA), FuGENE (Boehringer Mannheim Co, IN), Lipofectin, LipofectAMINE (Life Technologies Inc, MD) reagents and Calcium phosphate (CA-PO4) transfection. Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA. Each bar represents the mean of results from one experiment (triplicate).

30      **Figure 13** shows hAAT secretion from mouse liver transduced with rAAV. C57B1/6 mice were injected with either p43CB-AT, C-AT or E-AT vector either by portal vein or tail vein injection. PV=portal vein injection. TV=tail vein injection.

Figure 14 shows serum hAAT levels in C57Bl/6 mice after intratracheal (IT) injection of C-AT or p43CB-AT vector. Mice received either  $10^9$  IU of C-AT (open circles),  $10^9$  IU of p43CB-AT (open triangles) or  $10^{10}$  IU of p43CB-AT (open squares).

5       Figure 15 shows a map and nucleotide sequence for the vector of the present invention designated as C-AT.

Figure 16 shows a map and nucleotide sequence for the vector of the present invention designated as E-AT.

10      Figure 17 shows a map and nucleotide sequence for the vector of the present invention designated as dE-AT.

Figure 18 shows a map and nucleotide sequence for the vector of the present invention designated as p43C-AT.

15      Figure 19 shows a map and nucleotide sequence for the vector of the present invention designated as p43C-AT-IN. This vector includes intron II from human AAT gene to enhance transcription.

Figure 20 shows a map and nucleotide sequence for the vector of the present invention designated as p43CB-AT.

Figure 21 shows a map and nucleotide sequence for the vector of the present invention designated as C-AT2.

20      Figure 22 shows a map and nucleotide sequence for the vector of the present invention designated as p43msENC-AT. This vector is similar to p43C-AT but also comprises an enhancer sequence upstream of the CMV promoter.

Figure 23 shows a map and nucleotide sequence for the vector of the present invention designated as p43rmsENC-AT. This vector is the same as the p43msENC-AT vector except that the enhancer sequence is in an opposite orientation.

25      Figure 24 shows a map and nucleotide sequence for the vector of the present invention designated as p43msENCB-AT. This vector is similar to p43CB-AT but also comprises an enhancer sequence upstream of the CMV promoter.

Figure 25 shows a map and nucleotide sequence for the vector of the present invention designated as p43rmsENCB-AT. This vector is the same as p43msENCB-AT except that the enhancer sequence is in an opposite orientation.

Detailed Disclosure of the Invention

The subject invention pertains to novel materials and methods for providing gene therapy to a mammal or human having a condition or disorder, such as genetic deficiency disorders, where high levels of expression of a protein are required to treat the disorder or condition. In one method of the subject invention, a viral vector is introduced into cells of an animal wherein a therapeutic protein is produced, thereby providing genetic therapy for the animal. In one embodiment, a method of the invention comprises introducing into an animal cell or tissue an effective amount of viral particles or vector comprising a recombinant genome which includes heterologous polynucleotide encoding a protein useful in genetic therapy and that can be expressed by the cell or tissue. Expression of the heterologous polynucleotide results in production of the protein. Preferably, the therapeutic protein encoded by the heterologous polynucleotide is a serum protein. In a preferred embodiment, vector material comprising the heterologous polynucleotide is integrated into a chromosome of the cell of the host animal.

In one embodiment, a recombinant polynucleotide vector of the present invention is derived from adeno-associated virus (AAV) and comprises a constitutive or regulatable promoter capable of driving sufficient levels of expression of the heterologous DNA in the viral vector. Preferably, a recombinant vector of the invention comprises inverted terminal repeat sequences of AAV, such as those described in WO 93/24641. In a preferred embodiment, a vector of the present invention comprises polynucleotide sequences of the pTR-UF5 plasmid. The pTR-UF5 plasmid is a modified version of the pTR<sub>BS</sub>-UF/UF1/UF2/UFB series of plasmids (Zolotukhin *et al.*, 1996). The pTR-UF5 plasmid contains modifications to the sequence encoding the green fluorescent protein (GFP).

Promoters useful with the subject invention include, for example, the cytomegalovirus immediate early promoter (CMV), the human elongation factor 1-alpha promoter (EF1), the small nuclear RNA promoters (Ula and Ulb),  $\alpha$ -myosin heavy chain promoter, Simian virus 40 promoter (SV40), Rous sarcoma virus promoter (RSV), adenovirus major late promoter,  $\beta$ -actin promoter and hybrid regulatory element comprising a CMV enhancer/ $\beta$ -actin promoter. These promoters have been shown to be active in a wide range of mammalian cells. In addition to the natural promoters described above, synthetic promoters can be used in the present invention. For example, a synthetic

enhancer randomly assembled from Spc5-12-derived elements including muscle-specific elements, serum response factor binding element (SRE), myocyte-specific enhancer factor-1 (MEF-1), myocyte-specific enhancer factor -2 (MEF-2), transcription enhancer factor-1 (TEF-1) and SP-1 (Li et al., 1999; Deshpande *et al.*, 1997; Stewart *et al.*, 1996; Mitchell *et al.*, 1989; Briggs *et al.*, 1986; Pitluk *et al.*, 1991) can be used in vectors of the invention.

The promoters are operably linked with heterologous DNA encoding the protein of interest. By "operably linked," it is intended that the promoter element is positioned relative to the coding sequence to be capable of effecting expression of the coding sequence.

Promoters particularly useful for expression of a protein in muscle cells include, for example, hybrid CMV/β-actin promoters, CMV promoters, synthetic promoters and EF1 promoter. Promoters particularly useful for expression of a protein in liver cells include, for example, hybrid CMV/β-actin promoters and EF1 promoters.

Also contemplated for use with the vectors of the present invention are inducible and cell type specific promoters. For example, Tet-inducible promoters (Clontech, Palo Alto, CA) and VP16-LexA promoters (Nettelbeck *et al.*, 1998) can be used in the present invention.

The vectors can also include introns inserted into the polynucleotide sequence of the vector as a means for increasing expression of heterologous DNA encoding a protein of interest. For example, an intron can be inserted between a promoter sequence and the region coding for the protein of interest on the vector. Introns can also be inserted in the coding regions. Transcriptional enhancer elements which can function to increase levels of transcription from a given promoter can also be included in the vectors of the invention. Enhancers can generally be placed in either orientation, 3' or 5', with respect to promoter sequences.

Heterologous polynucleotide in the recombinant vector can include, for example, polynucleotides encoding normal, functional proteins which provide therapeutic replacement for normal biological function in animals afflicted with genetic disorders which cause the animal to produce a defective protein, or abnormal or deficient levels of that protein. Proteins, and the polynucleotide sequences that encode them, which can be provided by gene therapy using the subject invention include, but are not limited to, anti-

proteases, enzymes, structural proteins, coagulase factors, interleukins, cytokines, growth factors, interferons, and lymphokines. In an exemplified embodiment, heterologous DNA in a recombinant AAV vector encodes human alpha-1-antitrypsin protein.

The gene therapy methods of the invention can be performed by *ex vivo* or *in vivo* treatment of the patient's cells or tissues. Cells and tissues contemplated within the scope of the invention include, for example, muscle, liver, lung, skin and other cells and tissues that are capable of producing and secreting serum proteins. The vectors of the invention can be introduced into suitable cells, cell lines or tissue using methods known in the art. The viral particles and vectors can be introduced into cells or tissue *in vitro* or *in vivo*. Methods contemplated include transfection, transduction, injection and inhalation. For example, vectors can be introduced into cells using liposomes containing the subject vectors, by direct transfection with vectors alone, electroporation or by particle bombardment. In an exemplified embodiment, muscle cells are infected *in vivo* by injection of viral particles comprising recombinant vector into muscle tissue of an animal. In another embodiment, liver cells are infected *in vivo* by injection of recombinant virus into either the portal vein or peripheral veins.

The methods and materials of the subject invention can be used to provide genetic therapy for any conditions or diseases treatable by protein or cytokine infusion such as, for example, alpha-1-antitrypsin deficiency, hemophilia, adenosine deaminase deficiency, and diabetes. The methods and materials of the subject invention can also be used to provide genetic therapy for treating conditions such as, for example, cancer, autoimmune diseases, neurological disorders, immunodeficiency diseases, and bacterial and viral infections. For example, the present invention can be used to provide genetic therapy to a patient wherein cells from the patient are transformed to express and produce interleukins such as interleukin-2.

Animals that can be treated with the materials and methods of the invention include mammals such as bovine, porcine, equine, ovine, feline and canine mammals. Preferably, the mammals are primates such as chimpanzees and humans.

The subject invention also concerns cells containing recombinant vectors of the present invention. The cells can be, for example, animal cells such as mammalian cells. Preferably, the cells are human cells. More preferably, the cells are human myofibers or myoblasts, hepatocytes or lung cells. In a preferred embodiment, a recombinant vector

of the present invention is stably integrated into the host cell genome. Cell lines containing the recombinant vectors are also within the scope of the invention.

In an exemplified embodiment, recombinant AAV vectors comprising the human AAT gene (hAAT) using either the CMV promoter (AAV-C-AT) or the human elongation factor 1-alpha (EF1) promoter (AAV-E-AT) to drive expression were constructed and packaged using standard techniques. A murine myoblast cell line, C2C12, was transduced with each vector and expression of hAAT into the medium was measured by ELISA. *In vitro*, the EF1 promoter construct resulted in 10-fold higher hAAT expression than the CMV promoter construct. *In vivo* transduction was performed by injecting doses of up to  $1.4 \times 10^{13}$  Dnase-resistant particles of each vector into skeletal muscles of a number of different strains of mice (including C57B1/6, Balb/c, and SCID). *In vivo*, the CMV promoter construct resulted in higher levels of expression, with sustained serum levels up to 800  $\mu\text{g}/\text{ml}$  in SCID mice, approximately 10,000-fold higher than those previously observed with proteins secreted from AAV vectors in muscle. At lower doses in both C57B1/6 and SCID mice, expression was delayed for several weeks, but was sustained for over 10 weeks without declining. Thus, increasing dosage AAV vector via transduction of skeletal muscle provides a means for replacing AAT or other serum proteins.

Transduction of muscle using the vectors of the subject invention presents several advantages in that it is stable, non-toxic, and relatively nonimmunogenic. Furthermore, certain transcription promoters, such as the CMV promoter, which appear to be markedly down-regulated in other contexts have been found to remain active over time as used in the subject invention. Using the materials and methods of the subject invention, microgram/ml serum levels of a therapeutic protein can be achieved. In an exemplified embodiment, the levels of *in vivo* protein expression achieved represent a 10,000-fold or more increase over previously published results. In addition, a dose-effect relationship was demonstrable within the range of doses used, providing for further increases in expression levels as vector dose is increased.

In another embodiment of the invention, recombinant AAV vectors *i.e.*, C-AT, p43C-AT, P43CB-AT, E-AT and dE-AT comprising the human AAT gene (hAAT) using were constructed and packaged using standard techniques. A murine liver cell line, HO15, was transfected with each vector and expression of hAAT into the medium was

measured by ELISA. *In vitro*, transduction with the p43CB-AT vector exhibited the highest level of hAAT expression. *In vivo*, the p43CB-AT vector also gave higher levels of expression. Portal vein administration appeared to be the more efficient route of administration as mice injected in this manner exhibited higher levels of expression than those receiving peripheral vein injections. Transduction of liver offers the same advantages as for muscle, but hepatocytes may be more efficient at secretion of protein.

The dosage of recombinant vector or the virus to be administered to an animal in need of such treatment can be determined by the ordinarily skilled clinician based on various parameters such as mode of administration, duration of treatment, the disease state or condition involved, and the like. Typically, recombinant virus of the invention is administered in doses between  $10^5$  and  $10^{14}$  infectious units. The recombinant vectors and virus of the present invention can be prepared in formulations using methods and materials known in the art. Numerous formulations can be found in Remington's Pharmaceutical Sciences, 15<sup>th</sup> Edition (1975).

All publications and patents cited herein are expressly incorporated by reference.

#### Materials and Methods

**Construction of rAAV plasmids.** The rAAV-AAT vector plasmids used for these experiments are depicted diagrammatically (Figure 1). Briefly, the plasmid pN2FAT (Garver *et al.* (1987) plasmid was digested with *Xba*I to release 1.8-kb fragment containing the human AAT cDNA along with the SV40 promoter and a polyadenylation signal. This fragment was subcloned into a plasmid, pBlueScript (Stratagene) and, after the removal of the SV40 promoter by *Hind* III digestion and religation, the hAAT cDNA with its polyA signal was released by *Xba*I and *Xba*I digestion. This 1.4-kb *Xba*I-*Xba*I fragment was then cloned into the pTR-UF5 (an AAV-inverted terminal repeat-containing vector) plasmid (Zolotukhin *et al.*, 1996) between the *Xba*I site 3' to the CMV promoter and the *Xba*I site 5' to the polyoma virus enhancer/HSV thymidine kinase promoter cassette, which drives *neo* in that construct. This yielded the pAAV-CMV-AAT construct (C-AT). Analogous constructs using the promoter from the small nuclear RNA proteins, U1a and U1b, (to give the A-AT and B-AT constructs, respectively) and

human elongation factor 1-alpha (EF1) promoter (to give the E-AT construct) were constructed by substituting each of these promoter cassettes in place of the CMV promoter, between the KpnI and XbaI sites.

5       The construct, dE-AT derived from E-AT by deletion of the silencer (352 bp) by SAC II-cut (Wakabayashi-Ito *et al.*, 1994). C-AT2 is similar with C-AT except there are SV40 intron and poly (A) sequences flanking the cDNA of hAAT. The p43C-AT was constructed by insertion of hAAT cDNA to an AAV-vector plasmid (p43), which has CMV promoter, intron and poly (A) sequences. The p43CB-AT is derived by replacement of CMV promoter with CMV enhancer and chicken  $\beta$ -actin promoter sequences. The p43C-AT-IN is derived from p43C-AT by insertion of intron II sequences of hAAT gene to hAAT cDNA (Brantly *et al.*, 1995).

10      Packaging of rAAV vectors. Vectors were packaged using a modification of the method described by Ferrari *et al.* (1997). Briefly, plasmids containing the AAV *rep* and *cap* genes (Li *et al.*, 1997) and the Ad genes (E2a, E4 and VA-RNA) were co-transfected along with the appropriate AAV-AAT vector plasmid into 293 cells grown in Cell Factories (Nunc). Cells were harvested by trypsinization and disrupted by freeze-thaw lysis to release vector virions which were then purified by iodixanol gradient ultracentrifugation followed by heparin sepharose affinity column purification. Alternatively, recombinant virus can be prepared according to methods described in Zolotukhin *et al.* (1999).

15      Vector preparations had their physical titer assessed by quantitative competitive PCR and their biological titer assessed by infectious center assay. The presence of wild-type AAV was also assessed using these same assays with appropriate internal AAV probes. The high-dose C-AT stock had a particle-titer of  $2.0 \times 10^{14}$  particles/ml and an infectious titer of  $5.0 \times 10^{11}$  infectious units (i.u.)/ml (particle to i.u. ratio = 400:1). The low-dose C-AT measured  $8 \times 10^{12}$  particles/ml and  $1.2 \times 10^{10}$  i.u./ml (particle to i.u. = 667:1). For the E-AT experiments, the titers were  $1 \times 10^{13}$  particles/ml and  $2.5 \times 10^{10}$  i.u./ml (particle to i.u. = 400:1). The low-dose C-AT stock had a wt-like AAV particle titer (*i.e.*, positive AAV genome PCR) equal to 0.1 times the recombinant titer but no detectable infectious wtAAV. The other two preparations had wt-like AAV particle titers  $< 10^5$  times the recombinant titer and no detectable infectious wtAAV.

*In vitro transfection and transduction experiments.* The C2C12 murine myoblast line was used for *in vitro* transfection and transduction experiments. Cells were grown in 35-mm wells with approximately  $4 \times 10^5$  cells per well and transfected with 5  $\mu\text{g}$  of each plasmid DNA using Superfect (Qiagen Corp.). Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA assay with standards (Brantly *et al.*, 1991). An SV40 promoter luciferase-expression plasmid, pGL2 (Promega), was used as an internal control. For transduction experiments, cells were grown under similar conditions and were transduced with vector at multiplicities of infection ranging from  $4 \times 10^5$  to  $4 \times 10^6$  particles per cell. Cells were then passaged in the presence of geneticin sulfate (350  $\mu\text{g}/\text{ml}$ ) and geneticin-resistant clones were isolated for hAAT secretion studies.

*In vivo injection of AAV-C-AT and AAV-E-AT vectors into murine muscle.* Mice strains (C57B1/6, SCID, and Balb/c) were obtained from Jackson Laboratories (Bar Harbor, ME) and were handled under specific pathogen-free conditions under a protocol approved by the University of Florida Institutional Animal Care and Use Committee. Animals were anesthetized by metaphane inhalation and aliquots of vector were injected percutaneously into the quadriceps femoris muscles of both hind limbs. The volume of vector ranged from 50 to 100  $\mu\text{l}$  per injection site and the total amount of virus injected per animal ranged from  $5 \times 10^{10}$  to  $1.4 \times 10^{13}$  Dnase-resistant particles.

*Antigen capture ELISA assay for hAAT expression.* Microtiter plates (Immulon 4, Dynex Technologies, Chantilly, VA) were coated with 100  $\mu\text{l}$  of a 1:200 dilution of goat anti-human AAT (CAPPEL/ICN) in Vollers buffer ( $\text{Na}_2\text{CO}_3=2.76\text{g}$ ,  $\text{NaHCO}_3=1.916\text{g}$ ,  $\text{NaN}_3=0.2\text{g}$ , d. $\text{H}_2\text{O}=1$  liter, Adjust PH=9.6) overnight at 4°C. After washing, standards and unknown samples containing hAAT were incubated in the plates at 37°C for 1 hour. After blocking in 3% BSA in PBS-Tween 20 at 37°C for 1 hour, a second antibody (1:1000 dilution of rabbit anti-human AAT, Boehringer Mannheim) was reacted with the captured antigen at 37°C for 1 hour. Detection was performed using a third antibody incubation (1:800 dilution of goat anti-rabbit IgG-peroxidase conjugate, 37°C) followed by *o*-phenylenediamine (OPD, Sigma) detection and measurement of the absorbance at 490nm.

*ELISA assay for anti-hAAT and anti-AAV VP3 antibodies.* Wells were coated with antigen (1  $\mu\text{g}$  of hAAT or 100ng of VP3) at 4°C overnight, blocked with 3% BSA

and then reacted with dilutions of either test serum or with positive control antibodies at 37°C for 1 hour. After washing, a goat-anti-mouse IgG-peroxidase conjugate was used as a secondary antibody (1:1500 dilution) to detect bound anti-AAT antibody, using a standard OPD reaction, as described above. Antibody levels were quantitated by comparison with a standard curve generated by reacting dilutions of known positive monoclonal antibodies against VP3 and hAAT.

Lymphocyte proliferation assays to detect cell-mediated immune responses. Lymphocyte proliferation assays were performed in order to detect T cell responses to the hAAT and VP3 antigens. Freshly isolated splenocytes were grown in primary culture in 96 well plates coated with 0, 0.1, 1, and 10 µg of either hAAT or VP3 in RPMI-C+ medium. On day three, a pulse of <sup>3</sup>H-thymidine was added, and the cells were harvested on day 4 for lysis and scintillation counting. Phytohemagglutinin (PHA) was used as a mitogen for positive control wells. A stimulation index was calculated for each antigen dosage level by dividing the counts per minute (cpm) of <sup>3</sup>H-thymidine incorporated in the antigen-stimulated cells by the cpm in a control (unstimulated) well.

Following are examples which illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1 – *In vitro* studies in murine C2C12 myoblasts

In order to determine the relative strength of a number of constitutively active promoters in the context of AAV-AAT vectors, packageable AAV-AAT expression vectors containing one of the CMV, EF1, Ula or Ulb promoters (Figure 1) were constructed. Each of these constructs were transfected into the murine C2C12 myoblast cell line. Both the EF1 and the CMV promoter were active for AAT expression, with EF1 construct (AAV-E-AT) expressing 850 ng/10<sup>5</sup> cells/day and the CMV construct (AAV-C-AT) expressing approximately 670 ng/10<sup>5</sup> cells/day, as measured by a human-specific ELISA assay for AAT (Figure 2). This difference was not statistically significant. The levels of expression from the Ula and Ulb constructs were undetectable.

In order to better characterize the level and duration of expression in the setting of vector transduction, cultures of C2C12 cells were transduced with either AAV-E-AT

or AAV-C-AT at multiplicities of infection ranging from  $4 \times 10^5$  to  $4 \times 10^6$  Dnase-resistant particles per cell. Cells were then selected for expression of the *neo* gene (present in each of the AAV constructs) by growth in G418-containing medium. Several cell clones and pooled cell populations were independently analyzed for AAT expression at four weeks post-transduction (Figure 3). There was a clear trend toward higher levels of expression at higher multiplicities of infection, and the E-AT construct expressed at least 10-fold greater quantities under all conditions in these long-term cultures. The most active E-AT clone expressed hAAT at a rate of over 1400 ng/ $10^5$  cells/day.

10      Example 2—*In vivo* expression of hAAT from murine skeletal muscle

In order to determine whether the AAV-AAT constructs would be active *in vivo* in skeletal muscle, doses of vector were injected into the quadriceps femoris muscle of mice. Circulating serum levels of hAAT were then measured for 11 to 15 weeks after the initial injection. Four saline-injected animals from each mouse strain served as controls. 15      In the case of the C-AT vector (Figure 5A), levels of expression were sufficient to achieve serum levels in excess of 800  $\mu\text{g}/\text{ml}$  in SCID mice after a single injection of  $1.4 \times 10^{13}$  particles. A dose-effect relationship was observed, with expression levels in SCID being at least 20-fold lower at the  $5 \times 10^{11}$  particle dose. The levels of expression increased over the first several weeks after injection and were stable thereafter until the time of sacrifice. Since hAAT has a half-life of less than 1 week, this indicated continuous expression. Levels from C57B1/6 mice were comparable, and also achieved values close to the therapeutic range. In similar studies, two of three Balb/c mice injected with  $1 \times 10^{11}$  particles of the C-AT vector did not express hAAT at detectable levels. Both of these were found to have developed high levels of anti-hAAT antibodies. 20

25      Surprisingly, expression levels from the AAV-E-AT vector after *in vivo* injection were modestly lower than those seen with the C-AT vector (Figure 5B), with maximal levels of approximately 250 ng/ml at the  $5 \times 10^{11}$  dose at and beyond 7 weeks in SCID mice. When the dose was further increased to  $1 \times 10^{12}$  particles, levels of approximately 1200 ng/ml were observed. These levels were stable for one year post-injection (Figure 30      5C). Levels observed in SCID and immune competent C57B1/6 mice were similar.

Example 3 — Immunologic Studies

In studies in Balb/c mice, antibody levels against hAAT were high in 2 of 3 animals injected. The one which did not have circulating anti-hAAT was the only animal with levels of hAAT expression similar to those in the C57B1/6 and SCID groups. The 5 high-dose C57-C-AT injection group had detectable levels of antibody directed against VP3, but not hAAT.

In order to determine whether any cell-mediated immune responses were mounted, lymphocyte proliferation assays were performed using either hAAT or AAV-VP3 for antigenic stimulation of primary splenic lymphocytes harvested at the time of 10 animal sacrifice, 16 weeks post-vector injection. Using this method, no immune responses were detectable in any of the mice.

Example 4 — Lack of toxicity from direct vector injection

In order to determine whether there was any direct toxicity, inflammation, or 15 neoplastic change associated with vector injection, animals underwent complete necropsies. Histopathologic examination was performed on 5  $\mu\text{m}$  sections taken from the site of vector injection and from a panel of other organs, including the brain, heart, lungs, trachea, pancreas, spleen, liver, kidney, and jejunum. No histologic abnormalities 20 were observed in any of these sites, even among those mice which developed humanol immune responses against hAAT.

Example 5 — Molecular evidence of AAV-AAT vector persistence

To confirm the presence of vector DNA, a vector-specific PCR (*neo* primers 5'-TATGGGATCGGCCATTGAAC-3', and 5'-CCTGATGCTCTTC-GTCCAGA-3', was 25 performed on DNA extracted from 3 SCID mice 16 weeks after injection with the C-AT vector, and PCR products were analyzed by Southern blot analysis with a  $^{32}\text{P}$ -labeled vector-specific probe (Figure 8). The state of vector DNA was analyzed using the Hirt procedure (Carter *et al*, 1983) to separate the low molecular weight episomal DNA from the high molecular weight fraction, which would contain integrated forms and large 30 concatemers. In each case, vector DNA was present in the high molecular weight DNA fraction, whereas in only one of the animals was there a signal in the episomal fraction. This result indicates that by 16 weeks most of the vector DNA in our animals was either integrated or in large concatemers.

Example 6 — *In vivo* expression of hAAT from murine liver

Portal vein or tail vein injections were performed on 18 female C57BL/6 mice 8-10 weeks of age. The injection volume was 100 $\mu$ l per mouse.

Each group had the following parameters:

- 5        1.     Group 1: 100  $\mu$ l of PBS n=4.
2.     Group 2: 100  $\mu$ l of p43CB-AT (3x10<sup>10</sup> IU/animal) n=3.
3.     Group 3: 100  $\mu$ l of p43CB-AT (4x10<sup>9</sup> IU/animal) n=4.
4.     Group 4: 100  $\mu$ l of C-AT (4x10<sup>9</sup> IU/animal) n=2.
5.     Group 5: 100  $\mu$ l of E-AT (4x10<sup>9</sup> IU/animal) n=4.
- 10      6.     Group 6: EATM TV=100  $\mu$ l by tail vein injection of E-AT (4x10<sup>9</sup> IU/animal) n=3.
- 15      7.     Group 0: 100  $\mu$ l of PBS by tail vein injection n=2.

A total of 22 animals were used in this study.

All animals were anesthetized with 2-2-2 tribromoethanol (Avertin) using a working solution of 20 mg/ml at a dosage of 0.5 mg/g IP. A 2 cm ventral midline abdominal incision was made from the pubic symphysis extending cranially to the xiphoid process through skin and muscle layers. The portal vein was exposed by retracting the intestines and associated mesentery to the left side of the animal. Additionally, the quadrate and right medial lobes of the liver were retracted cranially.

20      Intestines and peritoneal cavity were continuously lavaged with 0.9% NaCl.

Virus or PBS was delivered into the portal vein using a 30 g needle attached to a 100  $\mu$ l capillary pipette using mouth delivery via rubber tubing and a Drummond self-locking double layer 0.8  $\mu$ m filter. A small piece of Gel-Foam (.5x.5cm) was applied to the injection site before the needle was removed from the portal vein. The needle was retracted from beneath the Gel-Foam and the piece was held in place with forceps while the intestines were replaced into the peritoneal cavity.

The muscle and skin were closed in one layer using 2 simple interrupted 3-0 nylon sutures on an FS-1 cutting needle. Surgeries were performed on a thermoregulated operating board designed to maintain a temperature of 37 degrees. For recovery from anesthesia, the animals were placed under a heat lamp adjusted to maintain an ambient temperature of approximately 37 degrees and given subcutaneous fluid if there was a significant amount of blood loss during surgery.

Serum levels of hAAT in the mice were measured two weeks after injection. Serum levels of about 200-150  $\mu\text{g}/\text{ml}$  hAAT were detected in mice receiving the p43CB-AT vector (Figure 13). Studies using the E-AT vector show that injection of vector by portal vein led to greater levels of hAAT secretion as compared to E-AT administered by tail vein injection.

5

**Example 7—*In vivo* expression of hAAT from murine lung**

10

Mice were injected intratracheally with either C-AT or p43CB-AT vector. Serum levels of hAAT in the mice were measured at day 3, 14 and 31 after injection (Figure 14). The p43CB-AT vector mediated high levels of expression of hAAT in lung.

15

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

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We claim:

Claims

- 1        1. A method for providing an animal with a therapeutically effective amount of  
2           a serum protein, said method comprising introducing into cells of said animal an effective  
3           amount of viral particles or vector, wherein said viral particles or viral vector comprises  
4           a polynucleotide encoding said protein.
  
- 1        2. The method according to claim 1, wherein said animal is a mammal.
  
- 1        3. The method according to claim 2, wherein said mammal is a human.
  
- 1        4. The method according to claim 1, wherein said vector is an adeno-associated  
2           virus vector.
  
- 1        5. The method according to claim 1, wherein said vector comprises a promoter  
2           sequence capable of driving expression of said polynucleotide encoding said protein.
  
- 1        6. The method according to claim 5, wherein said promoter sequence is selected  
2           from the group consisting of CMV promoter sequences, hybrid CMV enhancer/β-actin  
3           promoter sequences, EF1 promoter sequences, U1a promoter sequences and U1b  
4           promoter sequences.
  
- 1        7. The method according to claim 5, wherein said promoter sequence is an  
2           inducible promoter selected from the group consisting of Tet-inducible promoters and  
3           VP16-LexA promoters.
  
- 1        8. The method according to claim 5, wherein said vector further comprises an  
2           enhancer sequence.
  
  
- 1        9. The method according to claim 8, wherein said enhancer is a synthetic  
2           enhancer.

1           10. The method according to claim 1, wherein said animal has a condition that  
2       results in a defective protein or a deficiency of said protein encoded by said  
3       polynucleotide.

1           11. The method according to claim 1, wherein said animal has a condition that  
2       can be ameliorated or treated by said protein encoded by said polynucleotide.

1           12. The method according to claim 1, wherein said protein encoded by said  
2       polynucleotide is selected from the group consisting of anti-proteases, enzymes,  
3       structural proteins, coagulase factors, interleukins, cytokines, growth factors, interferons,  
4       and lymphokines.

1           13. The method according to claim 1, wherein said cells are myofibers,  
2       myoblasts, hepatocytes, or lung cells.

1           14. The method according to claim 1, wherein said polynucleotide encodes  
2       human alpha-1-antitrypsin protein, or a biologically active fragment or variant thereof.

1           15. The method according to claim 4, wherein said polynucleotide encodes  
2       human alpha-1-antitrypsin protein, or a biologically active fragment or variant thereof.

1           16. The method according to claim 1, wherein said viral particles are introduced  
2       into said cells or tissue by infection or injection.

1           17. The method according to claim 1, wherein said vector is introduced into said  
2       cells by transfection or injection.

1           18. The method according to claim 1, wherein said viral particles or vector is  
2       introduced into said cells *in vitro* and said treated cells are introduced into said animal.

1           19. The method according to claim 1, wherein said viral particles or vector is  
2 introduced into said cells *in vivo*.

1           20. The method according to claim 19, wherein said viral particles or vector is  
2 injected into muscle.

1           21. The method according to claim 19, wherein said viral particles or vector is  
2 injected into portal or peripheral vein.

1           22. The method according to claim 19, wherein said viral particles or vector is  
2 injected intratracheally or inhaled into the lungs.

1           23. The method according to claim 15, wherein said vector is selected from the  
2 group consisting of dE-AT, E-AT, C-AT, C-AT2, p43C-AT, p43CB-AT, p43C-AT-IN,  
3 p43msENC-AT, p43rmsENC-AT, p43msENCB-AT and p43rmsENCB-AT.

1           24. A recombinant viral vector comprising a polynucleotide encoding a protein  
2 capable of providing a therapeutic effect to an animal when expressed in said animal.

1           25. The vector according to claim 24, wherein said animal is a mammal.

1           26. The vector according to claim 25, wherein said mammal is a human.

1           27. The vector according to claim 26, wherein said vector is an adeno-associated  
2 virus vector.

1           28. The vector according to claim 24, wherein said vector comprises a promoter  
2 sequence capable of driving expression of said polynucleotide encoding said protein.

1           29. The vector according to claim 24, wherein said promoter sequence is selected  
2 from the group consisting of CMV promoter sequences, hybrid CMV enhancer/β-actin

3 promoter sequences, EF1 promoter sequences, Ula promoter sequences and U1b  
4 promoter sequences.

1 30. The vector according to claim 24, wherein said polynucleotide encodes  
2 human alpha-1-antitrypsin protein, of a biologically active fragment or variant thereof.

1 31. The vector according to claim 27, wherein said polynucleotide encodes  
2 human alpha-1-antitrypsin protein, of a biologically active fragment or variant thereof.

1 32. The vector according to claim 31, wherein said vector is selected from the  
2 group consisting of dE-AT, E-AT, C-AT, C-AT2, p43C-AT, p43CB-AT, p43C-AT-IN,  
3 p43msENC-AT, p43rmsENC-AT, p43msENCB-AT and p43rmsENCB-AT.

1 33. A viral particle comprising the vector of claim 24.

1 34. A cell comprising the vector of claim 24.

1 35. The cell according to claim 34, wherein said cell is a myofiber, myoblast,  
2 hepatocyte, or lung cell.

1 36. A method for treating alpha-1-antitrypsin deficiency in an animal, said  
2 method comprising introducing into cells of said animal a vector according to claim 24,  
3 wherein said polynucleotide of said vector encodes alpha-1-antitrypsin protein, or a  
4 biologically active fragment or variant thereof.

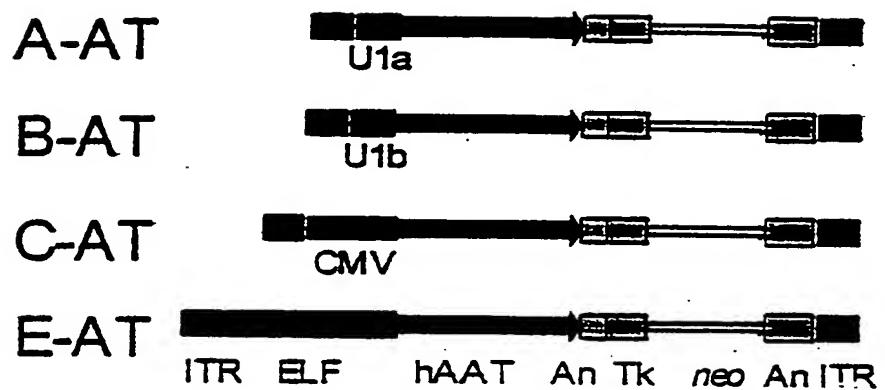


FIGURE 1

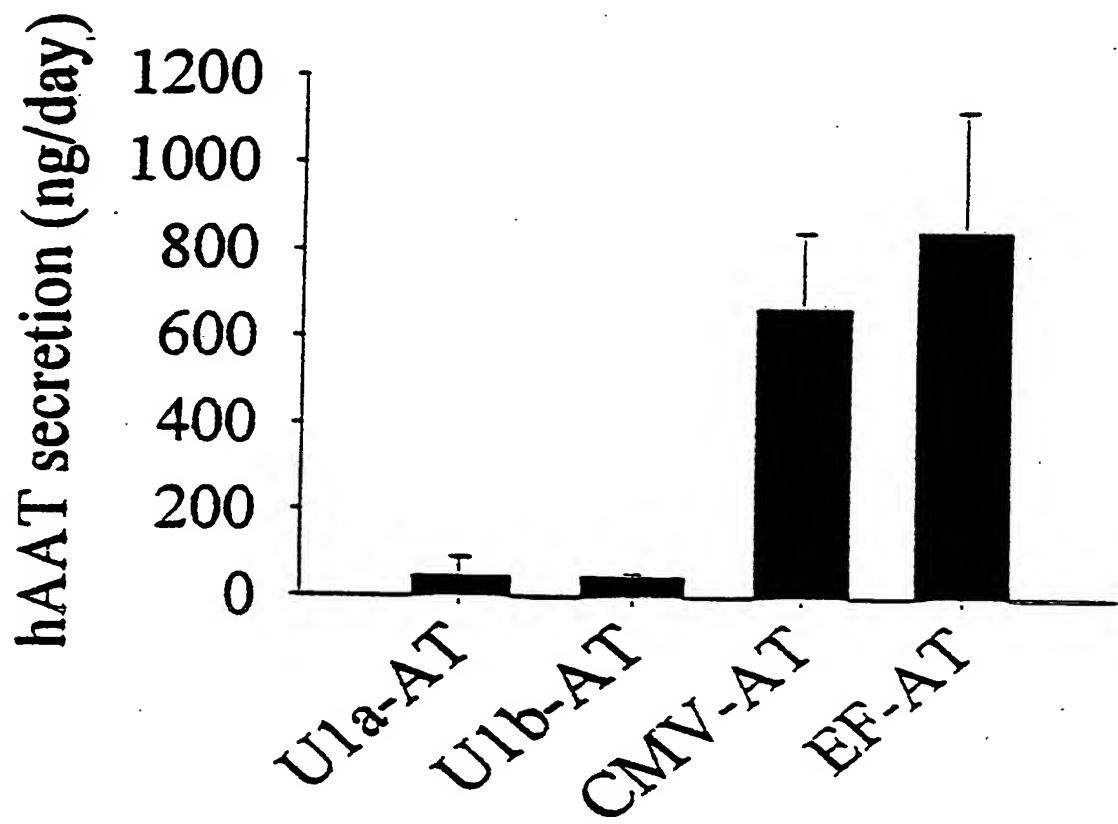


FIGURE 2

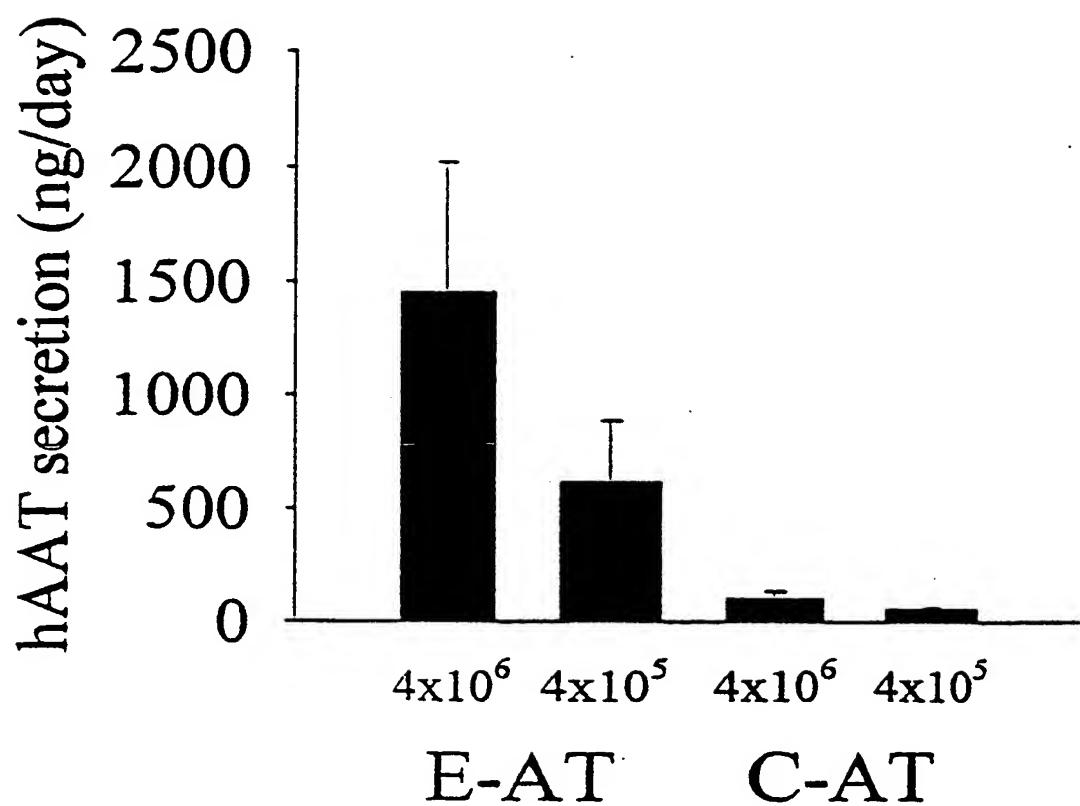


FIGURE 3

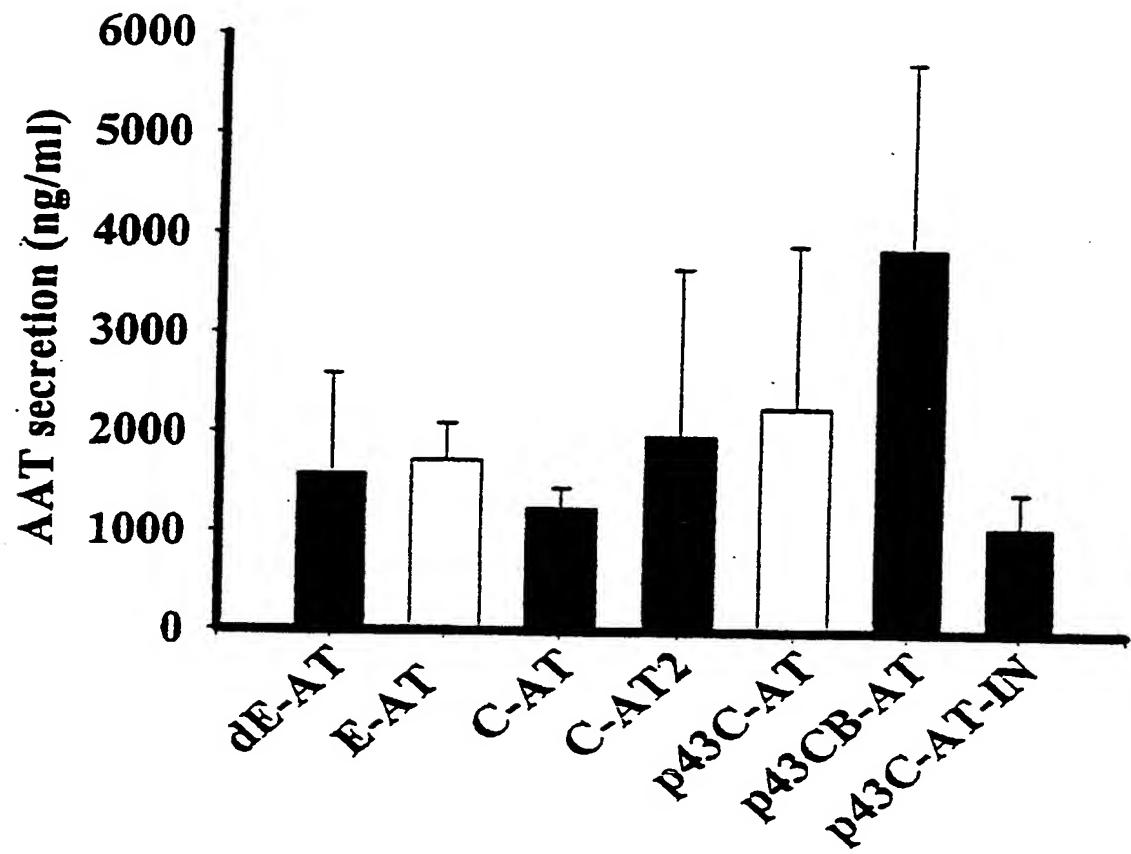


FIGURE 4

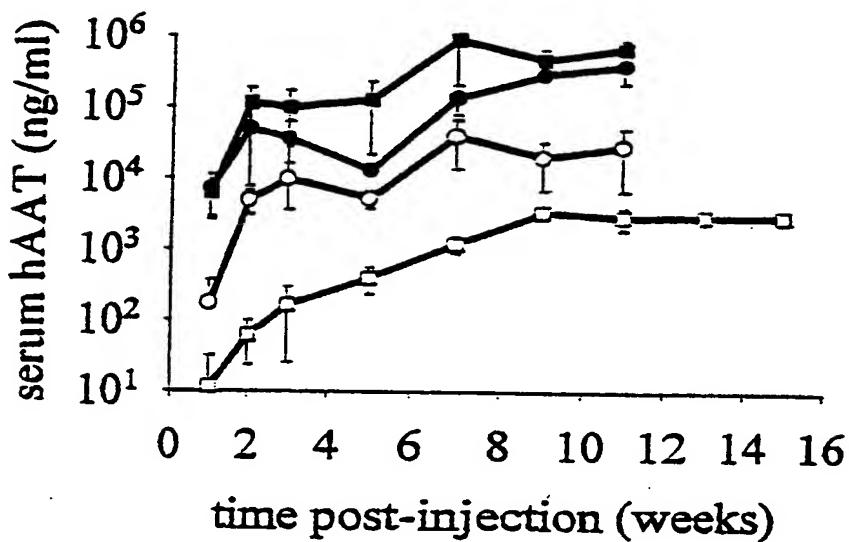


FIGURE 5A

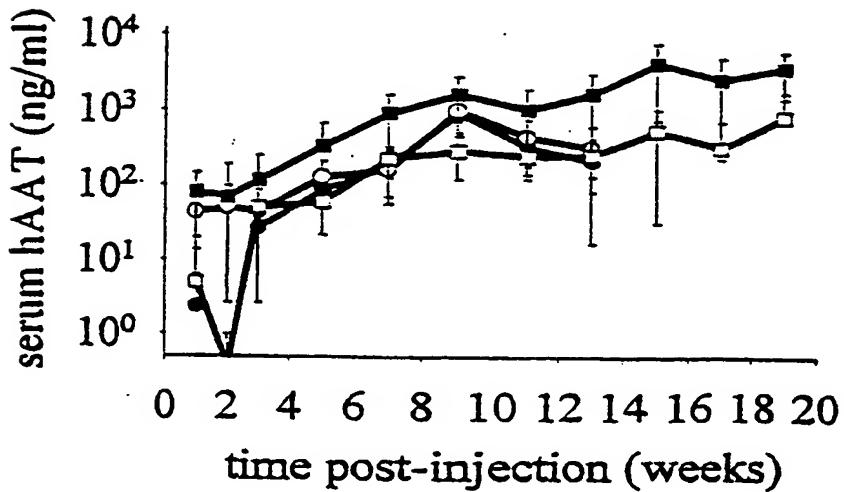


FIGURE 5B

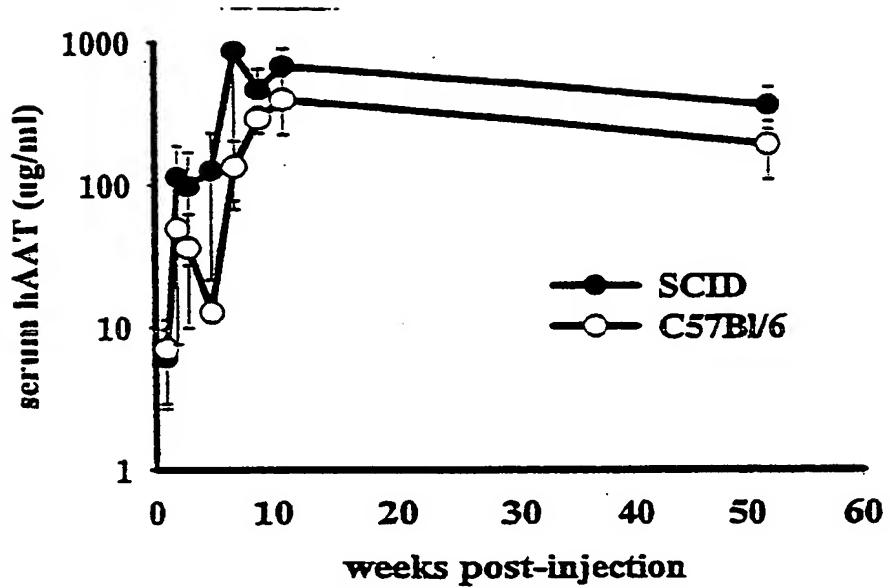


FIGURE 5C

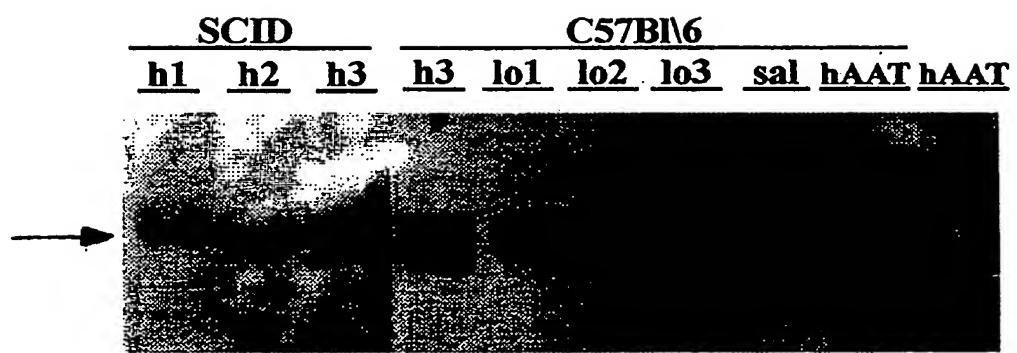


FIGURE 6

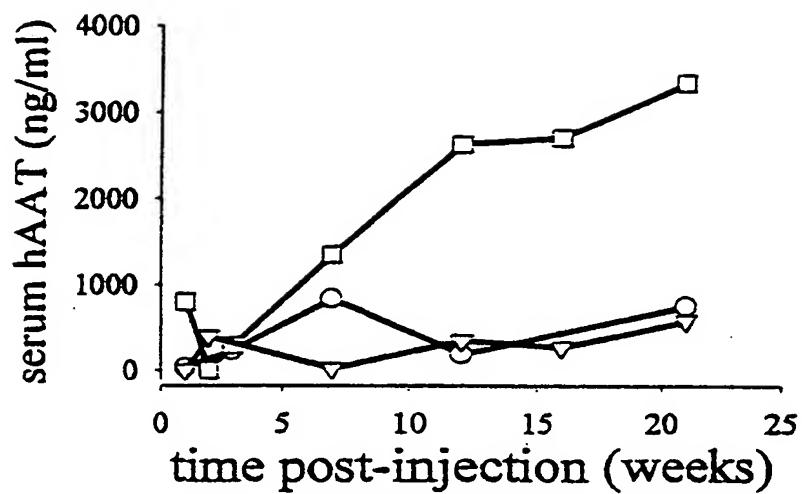


FIGURE 7A

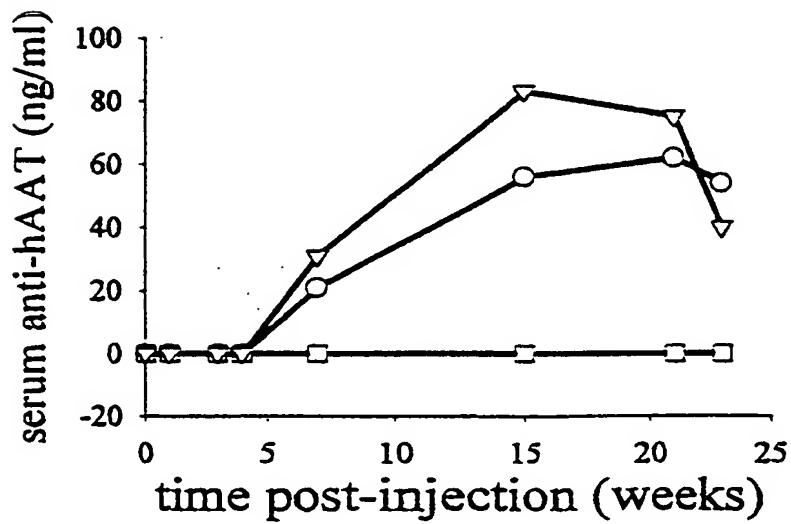


FIGURE 7B

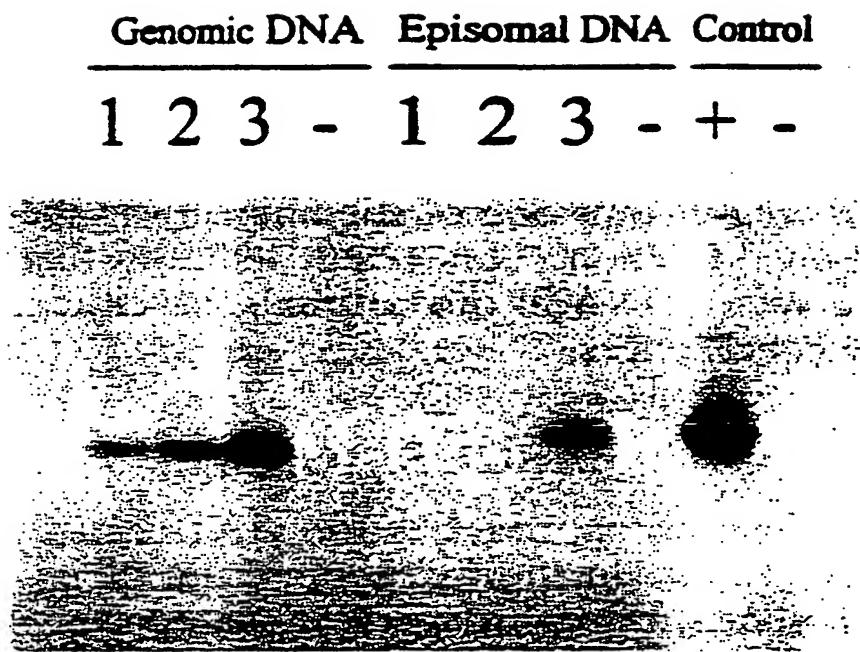


FIGURE 8

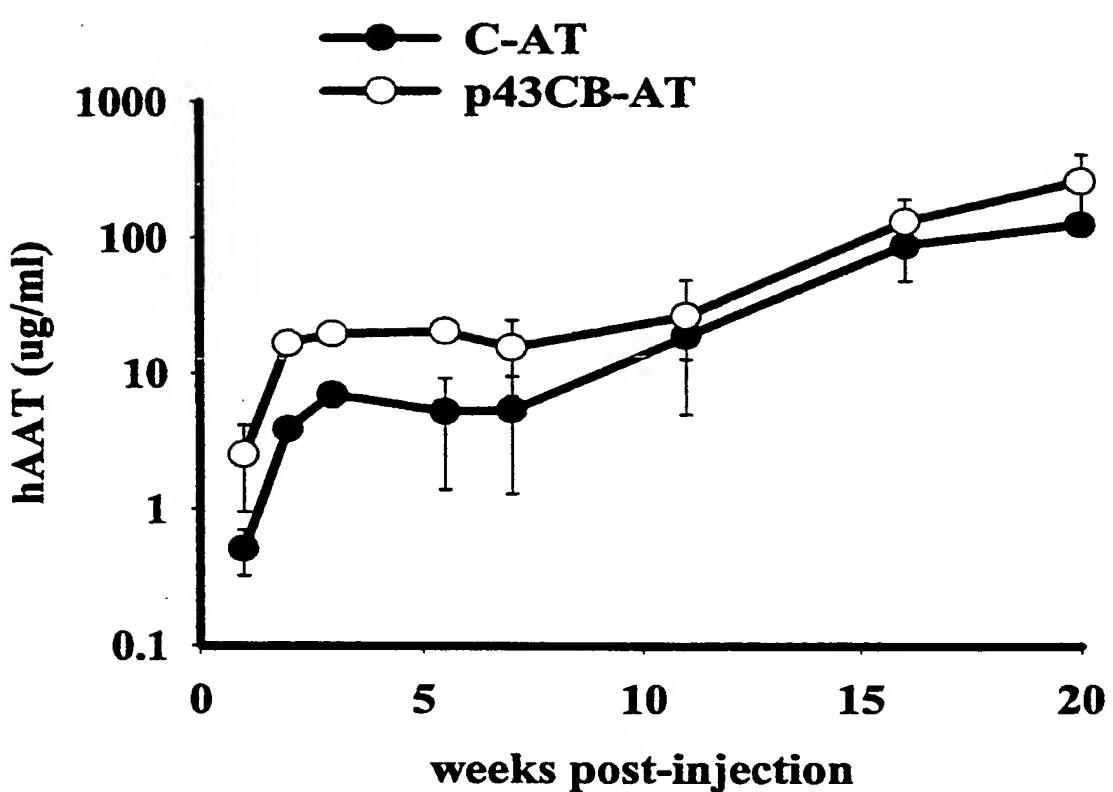


FIGURE 9

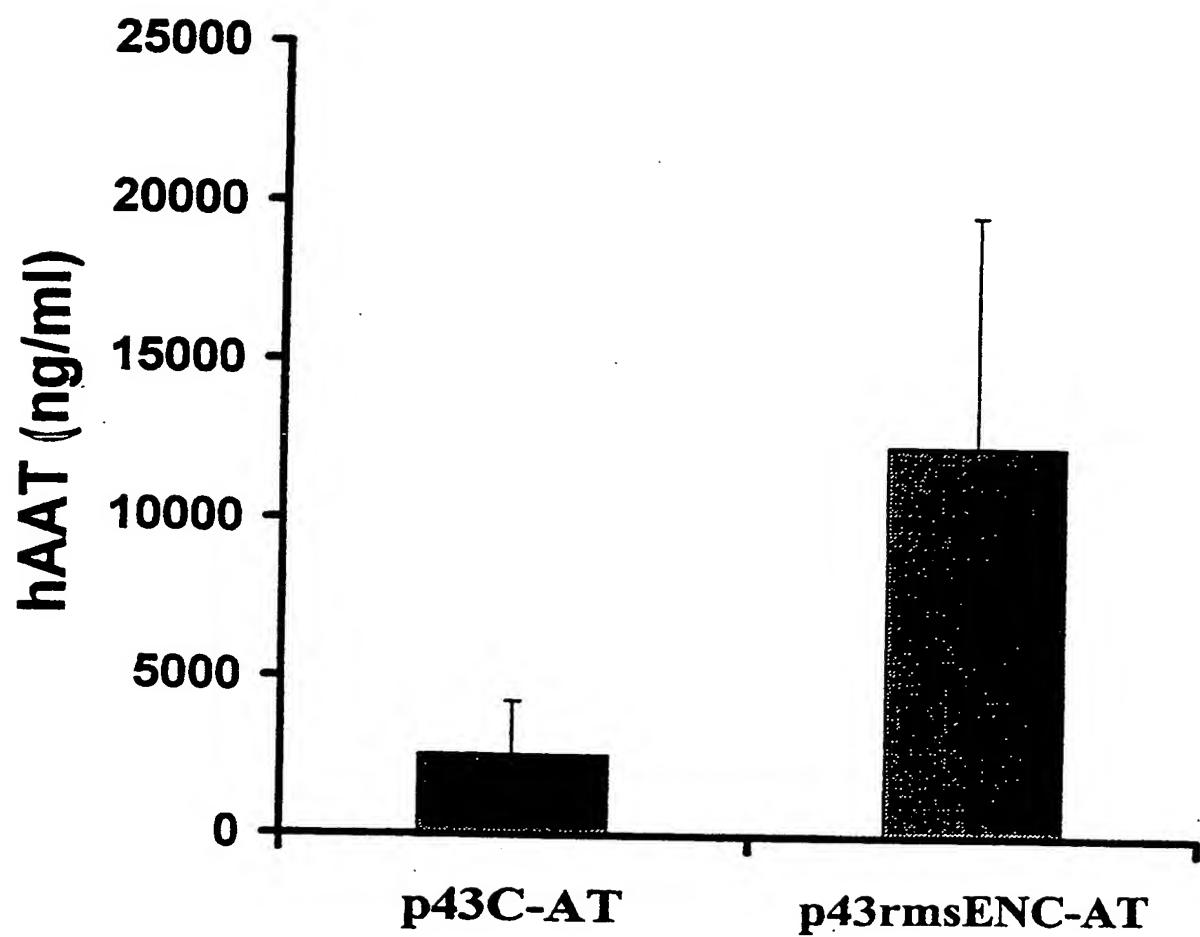


FIGURE 10

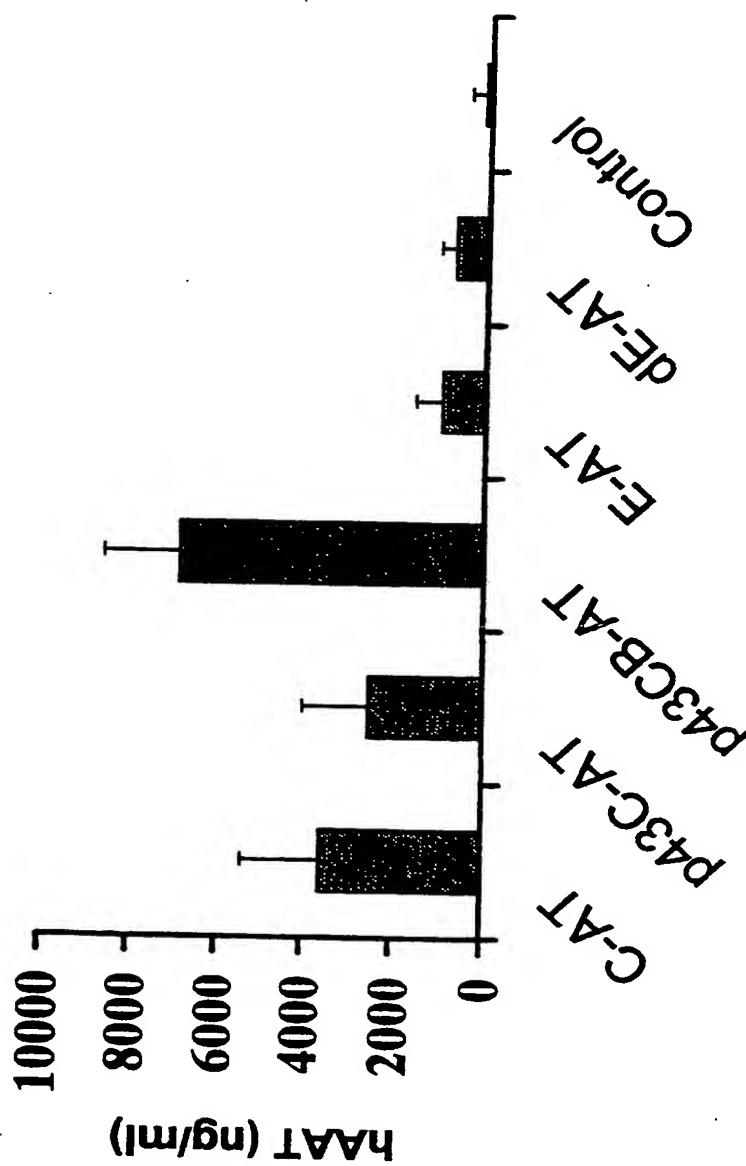


FIGURE 11

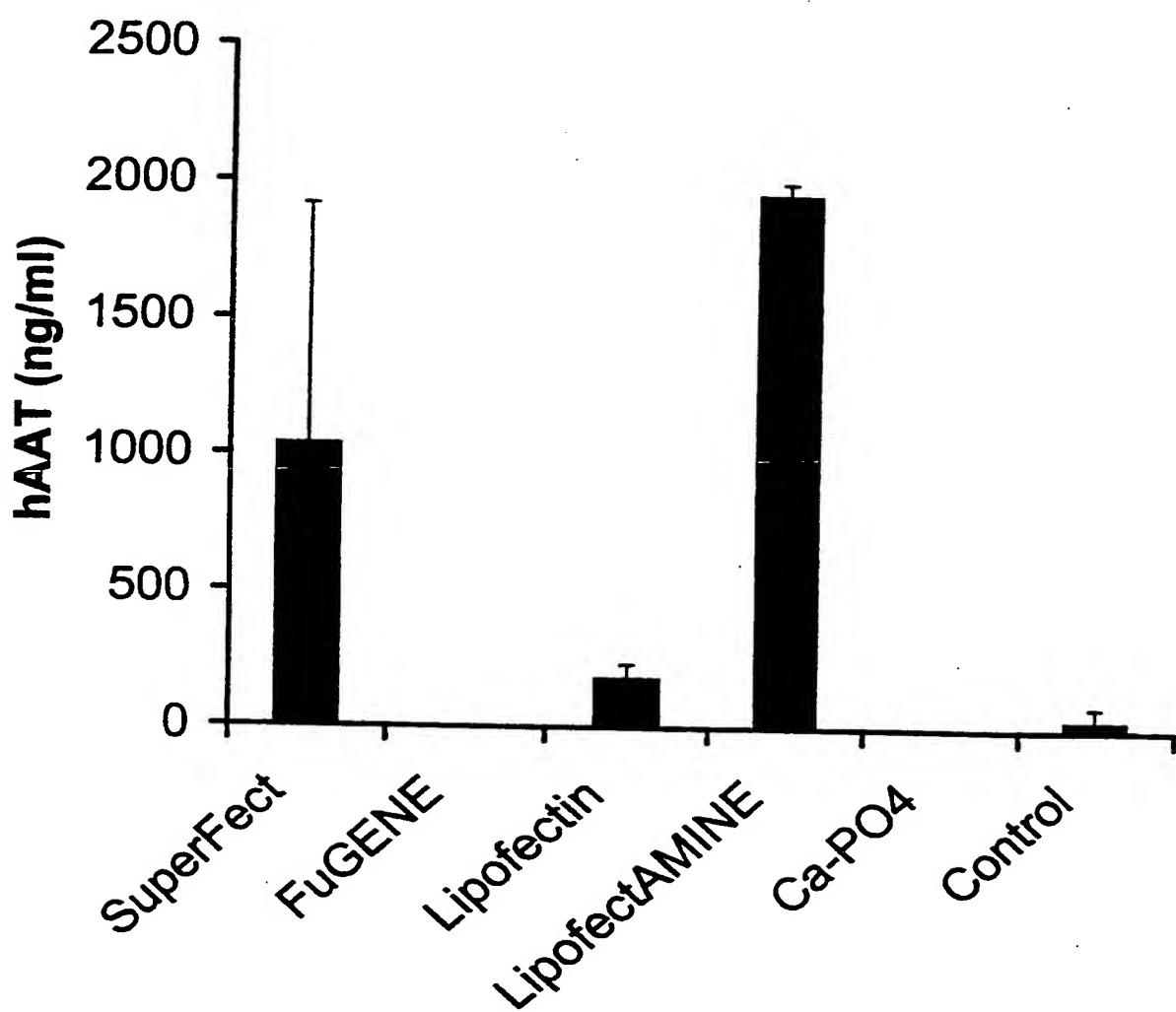


FIGURE 12

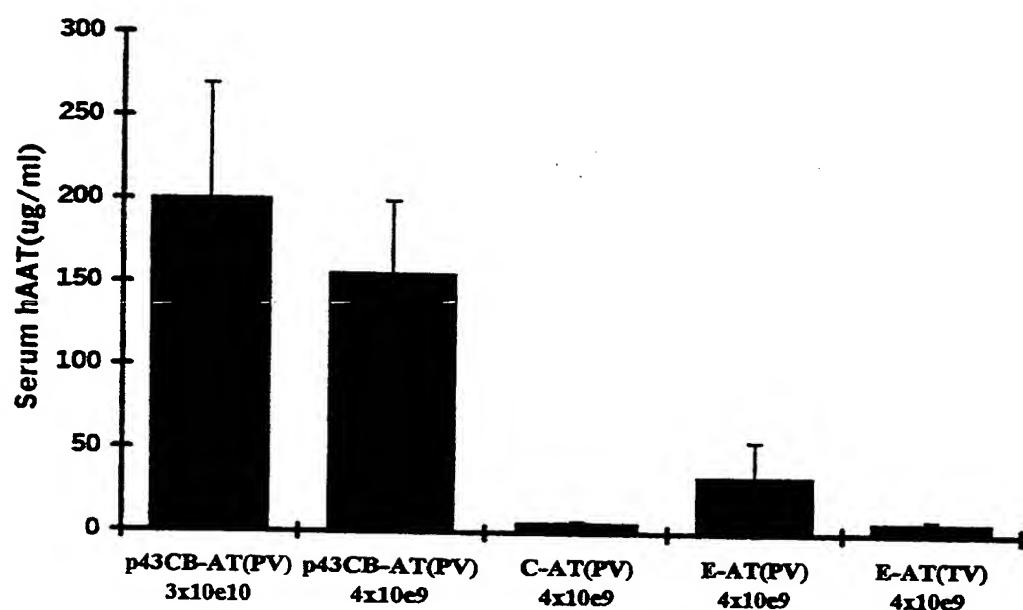


FIGURE 13

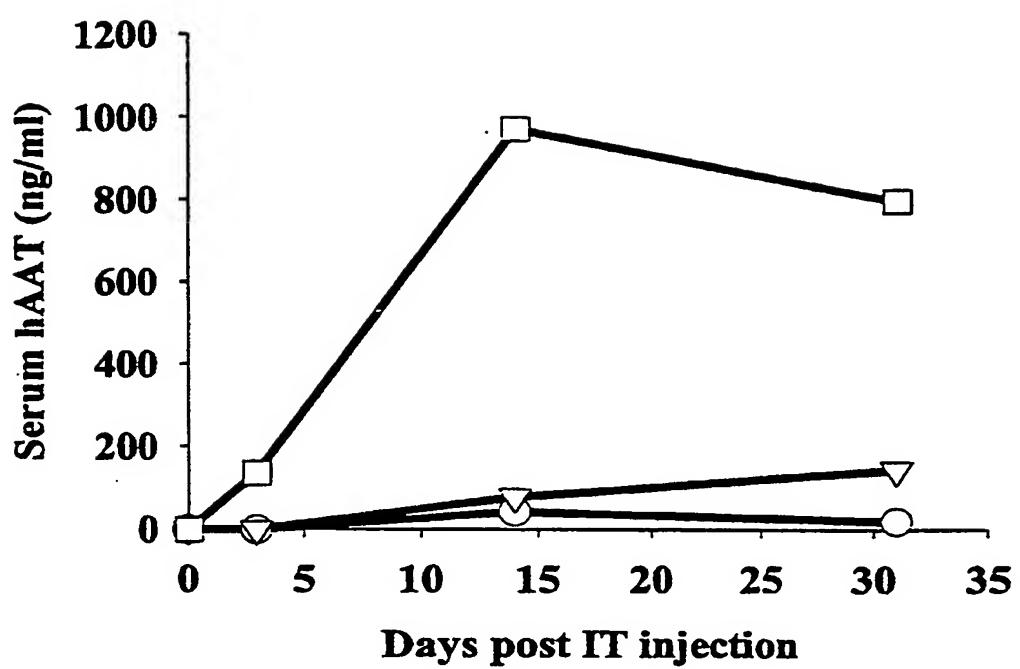


FIGURE 14

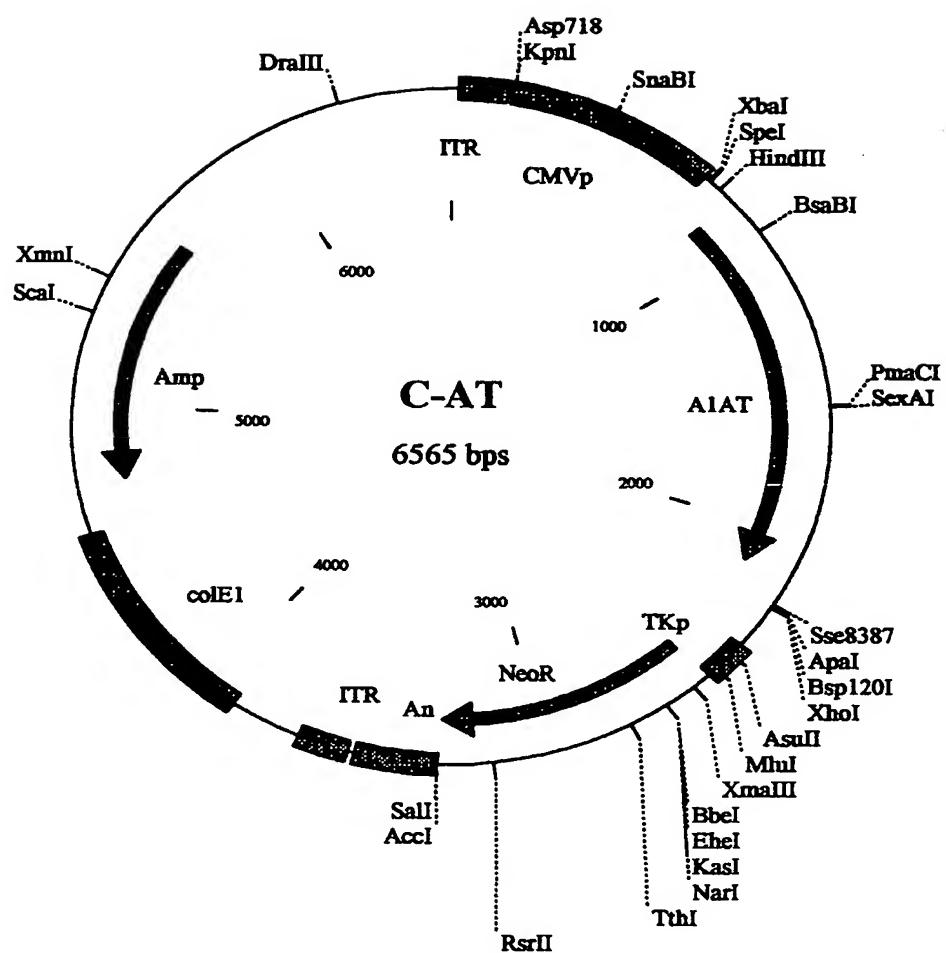


FIGURE 15

Molecule Name: C-AT 6565 bps DNA Circular  
Sequence Printed: 1-6565 (Full) Date Printed 16 Apr 1999  
Description: Ligation of ptr and aat

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51 cactgaggcc gggcgaccaa aggtcgcccc agccccggc tttgccccggg  
101 cggcctcagt gagcgagcga gcgcgcagag agggagtggc caactccatc  
151 actaggggtt cctagatctg aattcggtag ccgttacata acttacgta  
201 aatggcccgc ctggctgacc gcccAACGAC ccccggccat tgacgtcaat  
251 aatgacgtat gttcccatag taacgccaat agggacttgc cattgacgtc  
301 aatgggtgga gtatttacgg taaactgccc acttggcagt acatcaagtg  
351 tatcatatgc caagtacgcc ccctattgac gtcaatgacg gtaaaatggcc  
401 cgccctggcat tatgcccagt acatgacett atgggacttt cctacttggc  
451 agtacatcta cgtattagtc atcgcttata ccatggtgat gcggtttgg  
501 cagtacatca atgggcgtgg atagcggtt gactcacggg gatttccaag  
551 tctccacccc attgacgtca atgggagtt gtttggcac caaaatcaac  
601 gggactttcc aaaatgtcgt aacaactccg ccccattgac gcaaattggc  
651 ggttaggcgtg tacgggtggga ggtctatata agcagagctc gtttagtggaa  
701 cgcgtcagatc gcctggagac gccatccacg ctgttttgc  
751 gacaccggga ccgatccagc ctcggactc tagaactagt ggatcccccg  
801 ggctgcagga attcgtatc aagttttttt attttcaggc accaccactg  
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901 cctgctggca ggcctgtgt gcctggtccc tgctcctg gctgaggatc  
951 cccagggaga tgctgcccag aagacagata catccccca tgcaggatc  
1001 cacccaaacct tcaacaagat caccggcaac ctggctgagt tcgccttcag  
1051 cctataccgc cagctggcac accagtccaa cagcaccaat atcttcttct  
1101 ccccagttag categctaca gcctttgcaa tgctctccct ggggaccaag  
1151 gctgacactc acgatgaaat cctggaggcc ctgaatttca acctcacgga  
1201 gattccggag gtcagatcc atgaaggctt ccaggaactc ctccgtaccc  
1251 tcaaccagcc agacagccag ctccagctga caccggcaaa tggctgttc  
1301 ctcagcgagg gcctgaagct agtggataag ttttggagg atgttaaaaa  
1351 gttgtaccac tcagaagcc tcactgtcaa ctcggggac accgaagagg  
1401 ccaagaaaaca gatcaacgat tacgtggaga agggtaactca agggaaaatt  
1451 gtggatttgg tcaaggagct tgacagagac acagttttg ctctggtgaa  
1501 ttatcatcttc ttaaaaggca aatgggagag accctttgaa gtcaggaca  
1551 ccgaggaaga ggacttccac gtggaccagg tgaccacgt gaaggtgcct  
1601 atgatgaagc gtttaggcatt tttaaacatc cagactgt aaaaaaaaaa  
1651 cagctgggtg ctgctgtatga aataacctggg caatgcccaccc  
1701 tcctgcotga tgagggggaaa ctacagcacc gcatcttct  
1751 gatatcatca ccaagttccct gggaaaatgaa tgaccacgt  
1801 acatttaccc aaactgtcca ttactggaa ctatgtcc  
1851 tgggtcaact gggcatcaact aaggcttca gcaatggggc  
1901 ggggtcacag aggaggcacc cctgaagctc tccaaaggcc  
1951 tgtgctgacc atcgacgaga aaggactga agtgcgtgg  
2001 tagaggccat acccatgtct atcccccccg gcatgttt  
2051 tttgtcttct taatgattga aaaaaataacc aggtcaagtt  
2101 aaaagtggtg aatccccaccc aaaataact aagtctcccc  
2151 tccccctccat ccctggcccc ctcctggat gcatattaaag  
2201 ctggtaaccc ccccccccccc tgcagggggcc aagggtttgag  
2251 aagaggaagc aaaaagectc tccacccagg ctcgagcagt  
2301 gtgcgaaggca gtgtggttt gcaagaggaa  
2351 ggcctggaaat gttccaccc aatgtcgagc  
2401 cattggcgaat ttcgaacacg cagatgcgt  
2451 tccacttcgc atattaaggat gacgcgtgt  
2501 ctgcagccaa tatggatcg gccattgaac  
2551 tctccggccg cttgggtgg aaggcttattc  
2601 gacaatcggc tgctctgtatc  
2651 gccccgttct tttgtcaag accgacctgt  
2701 caggacgagg cagcgcggct atcgtggctg

**FIGURE 15A**

18 / 59

2751 cgcagctgtg ctgcacgttg tcactgaagc gggaaaggac tggctgctat  
 2801 tggcgaaagt gccggggcag gatccctgt catctcacct tgctctgcc  
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 2901 tccggctacc tccccattcg accaccaagc gaaacatcgc atcgagcag  
 2951 cacgtactcg gatggaaagg ggtcttgcg atcaggatga tctggacgaa  
 3001 gagcatcagg ggctcgccc agccgaactg ttccgcaggc tcaaggcgcg  
 3051 catgcccac ggcgaggatc tcgtcgtgac ccatggcgat gcctgcttgc  
 3101 cgaatatcat ggtggaaaat ggccgtttt ctggattcat cgactgtggc  
 3151 cggctgggtg tggcggaccg ctatcaggac atagcgttgg ctacccgtga  
 3201 tattgtgaa gagcttggcg gcgaatgggc tgaccgttc ctcgtgttgc  
 3251 acggtatcgc cgctcccgat tcgcagcga tgcgttcta tcgccttctt  
 3301 gacgagttt tctgagggga tccgtcact agagctcgat gatcagccctc  
 3351 gactgtgcct tctagttgccc agccatctgt tggggccccc tcccccggtc  
 3401 cttcccttgc cctggaaagg gccaactccca ctgtcccttc ctaataaaat  
 3451 gaggaaattt catgcattt tctgagttgg tgcatttcta ttctgggggg  
 3501 tgggggtgggg caggacagca agggggagga ttggaaagac aatagcagggc  
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 3651 cggggcactt ttggcgccc ggctcagtgc agcgagcgag cgccgcagaga  
 3701 gggagtggcc aaaaaaaaaa ccccccccccc tgcagccctg cattaatgaa  
 3751 tcggccaaagc cgccggggaga ggccgtttgc gtattggcg ctcttcgc  
 3801 tcctcgctca ctgactcgat ggcgtcggtc gttcggctgc ggcgagcggt  
 3851 atcagctcac tcaaaggcgg taatacgggt atccacagaa tcaggggata  
 3901 acgcaggaaa gaacatgtga gaaaaaggcc agccaaaaggc caggaaccgt  
 3951 aaaaaggccg cgttgcgtggc gttttccat aggctccgccc ccctgacga  
 4001 gcatcacaaa aatcgacgct caagtccagag gtggcgaac ccgacaggac  
 4051 tataaagata ccaggcggtt cccctggaa gctccctgt ggcgttcet  
 4101 gttccgaccc tgccgttac cggataacctg tccgccttc tccttcggg  
 4151 aagcgtggcg ctttctcaat gtcacgctg taggtatctc agttcgggt  
 4201 aggtcgttcg ctccaagctg ggctgtgtgc acgaaccccc cgttcagcc  
 4251 gaccgctgcg ctttatccgg taactatcg tttgagtcga acccggttaag  
 4301 acacgactt tcgccactgg cagcagccac tggtaacagg attagcagag  
 4351 cgaggtatgt aggccgtgtc acagagttt tgaagtgtg gcctaactac  
 4401 ggctacacta gaaggacagt atttggtatac tgcgtctgc tgaagccagt  
 4451 taccttcgga aaaagagttt gtagcttttgc atccggcaaa caaaccaccc  
 4501 ctggtagcgg tggtttttt gtttgcaggc agcaggatc ggcagaaaa  
 4551 aaaggatctc aagaagatcc tttgatctt tctacgggt ctgacgctca  
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 4701 taaagtatat atgagtaaac ttggctgtac agttaccaat gcttaatcag  
 4751 tgaggcaccc atctcagcga tctgtctatt tcgttcatcc atagttgcct  
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 5251 tggcatccgt aagatgttt tctgtactg gtgagttactc aaccaagtca  
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 5351 acgggataat accgcgcac atagcagaac ttaaaatgt ctcataattt  
 5401 gaaaacgttc ttggggcga aaactctcaa ggatcttacc gctgttggaga  
 5451 tccagttcga tgtaacccac tcgtgcaccc aactgatctt cagcatctt  
 5501 tactttcacc agcggttctg ggtgagaaaa aacaggaagg caaatgccc  
 5551 caaaaaaggaa aataaggcgc acacggaaat gttgaataact catactttc  
 5601 cttttcaat attattgtaa catttatcag gttattgtc tcatgagcgg  
 5651 atacatattt gaatgtatgg agaaaaataa acaaataagg gttccgcga  
 5701 catttcccccaaaatgtccca cctgacgtct aagaaaccat tattatcatg

FIGURE 15B

5751 acattaacct ataaaaatag gcgtatcacg aggccttgc gtctcgcg  
5801 ttcggtgat gacggtgaaa acctctgaca catgcagctc ccggagacgg  
5851 tcacagcttgc tctgttaagcg gatgccggga gcagacaagc cggtcaggc  
5901 gcgtcagcgg gtgttggcgg gtgtcccccc tggcttaact atgcggcatc  
5951 agagcagatt gtactgagag tgaccatat gcggtgtgaa ataccgcaca  
6001 gatgcgttaag gagaaaatac cgcatcagga aattgttaaac gttaatattt  
6051 tgtaaaattt cgcgttaaat tttgttaaa tcagtcatt ttttaaccaa  
6101 taggcccggaaa tcggccaaaat cccttataaa tcaaaagaat agaccgagat  
6151 agggtttagt gttgttccag tttggAACAA gagtccacta ttaaagaacg  
6201 tggactccaa cgtccaaaggcg cgaaaaaccg tctatcaggg cgatggccca  
6251 ctacgtgaac catcacccta atcaagtttt ttgggggtcga ggtgccgtaa  
6301 agcactaaat cggaacccta aagggagccc cggatTTAGA gcttgacggg  
6351 gaaaggccggc gaacgtggcg agaaaggaaag ggaagaaagc gaaaggagcgc  
6401 ggcgcctaggcg cgctggcaag tgttagcggtc acgctgcgcg taaccaccac  
6451 acccgccgcg cttaatgcgc cgctacaggcg cggcgtcgccg cattcgccat  
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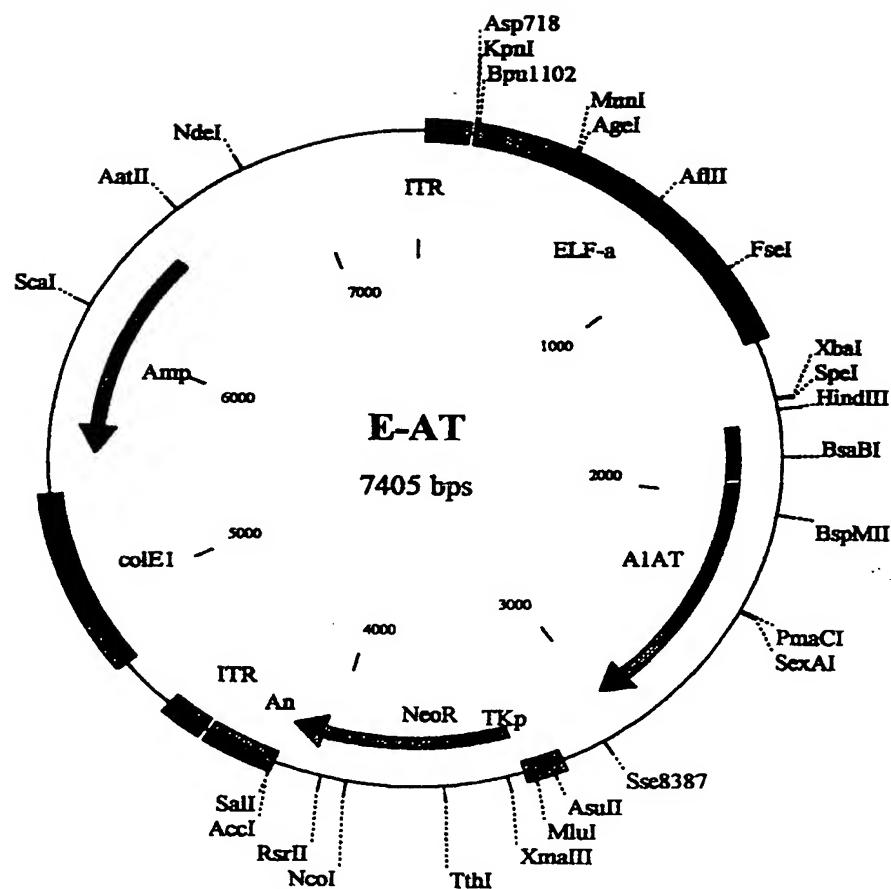


FIGURE 16

Molecule Name: E-A<sup>A</sup> 7405 bps DNA Circular  
 Sequence Printed: 1-7405 (Full) Date Printed 16 Apr 1999  
 Description: Ligation of AAT and elf

```

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101 cggccctcagt gagcgagcga gcgcgcagag agggagtggc caactccatc
151 actaggggtt cctagatctg aattcggtagt cttggagcta agccagcaat
201 ggttagagggaa agattctgcg cgtcccttcc aggccggctc cccgtcacca
251 ccccccccaa cccgcggcga cccggagctga gagaatcca tacaaaagga
301 ctcgcggcctg cttctgggaa tcccaggggac cgtcgttaaa ctcccactaa
351 cgtagaaccacc agagatcgct ggcgttccgc cccttcaccc gcccgcctc
401 gtcatcactg aggtggagaa gagcatgcgt gaggctccgg tgcccgtcag
451 tggcagagc gcacatcgcc cacagtcccc gagaagttgg ggggaggggt
501 cggcaattga accgggtgcct agagaagggtg ggcggggta aactggaaaa
551 gtatgtcgt gtactggctc cgccttttc ccgagggtgg gggagaaccg
601 tatataagtg cagtagtcgc cgtgaacgtt cttttcgca acgggtttgc
651 cgccagaaca caggttaagtg ccgtgtgtgg ttcccgcggg cctggctct
701 ttacgggtta tggcccttgc gtgccttgaa ttacttccac gcccctggct
751 gcagtagcgtg attcttgatc cccggatccgc ggttggaaagt ggggtggaga
801 gttcgaggcc ttgcgttaa ggagccccctt cgcctcgtgc ttgagttgag
851 gcctggcttgc ggcgtctgggg cccggcgctg cgaatctgtt ggcacccctcg
901 cgcctgtctc gtcgttttcg ataagtctt agccatttaa aattttgtat
951 gacctgtcgc gacgtttttt ttctggcaag atagtcttgc aaatgcgggc
1001 caagatctgc acactggtat ttgcgtttttt gggggccggg gggggcggcgg
1051 ggcccggtgcg tcccagcgca catgttcggc gagggggggc ctgcgagcgc
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1151 gtgcctggcc tcgcggccgc gtgtatcgcc cgcggccggg cggcaaggct
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1251 ctgtgcagg gagtcaaaaa tggaggacgc ggcgtcgccg agagcgggcg
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1351 ttcatgtgac tccacgggtt accggggcgcc gtccaggac ctcgattagt
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1501 ttggcacttg atgttaattct ctttggaaatt tggccctttt gaggttggat
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1601 tttcagggtgt cgtaaaaatc tagaactagt ggatcccccg ggctgcagga
1651 attcgatatac aagcttgggg attttcaggc accaccactg acctgggaca
1701 gtgaatcgac aatgcgtct tctgtctcg ggggcatect cctgtggca
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1901 cagctggcac accagtccaa cagcacaat atcttttctt ccccaatggag
1951 catcgctaca gcctttgcaa tgctctccct ggggaccaag gctgacactc
2001 acgatgaaat cctggagggc ctgaatttca acctcacggg gattccggag
2051 gctcagatcc atgaaggctt ccagggactc ctccgtaccc tcaaccagcc
2101 agacagccag ctccagctga ccaccggcaa tggcctgttc ctcagcgagg
2151 gcctgaagct agtggataag tttttggagg atgttaaaaaa gttgtaccac
2201 tcagaaggct tcactgtcaa ttccggggac accgaagagg ccaagaaaca
2251 gatcaacgat tacgtggaga agggtaatcga agggaaaatt gtggatgg
2301 tcaaggagct tgacagagac acatgttttgc ctctgtgaa ttacatctt
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2401 ggacttccac gtggaccagg tgaccacgtt gaaggtgcct atgatgaagc
2451 gtttaggcat gtttaacatc cagcaactgta agaagctgtc cagctgggtg
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2551 tgagggggaaa ctacagcacc tggaaaatga actcacccac gatatcatca
2601 ccaagttccct ggaaaatgaa gacagaagggt ctgcctgatc acatttaccc
2651 aaactgttcca ttactggaaac ctatgtatcga aagagcgtcc tgggtcaact
2701 gggcatcact aaggtttca gcaatggggc tgaccccttcc ggggtcacag

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FIGURE 16A

2751 aggaggcacc ccaagctc tccaaggccg tgcataggc ~~tgcgtgaac~~  
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 2851 accatgtct atcccccccg aggtcaagtt caacaaaacc cttgttct  
 2901 taatgattga aaaaaataacc aagtctccc tttcatggg aaaagtggtg  
 2951 aatcccaccc aaaaataact gcctctcgct cctcaacccc tcccctccat  
 3001 ccctggcccc ctccctggat gacattaaag aagggttgag ctggtaaccc  
 3051 cccccccccc tgcaggggcc ctcgagcagt gtggtttgc aagaggaagc  
 3101 aaaaaggctc tccacccagg cctggaaatgt ttccacccaa gtcgaaggca  
 3151 gtgtggttt gcaagaggaa gaaaaaagcc tttccacccaa ggcttggaaat  
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 3701 ccatcatggc t gatgcaatg cggcggtgtc atacgcttga tccggctacc  
 3751 tgcccatcg accaccaagg gaaacatcg atcagagcgag cacgtactcg  
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 5451 aactcacgtt aagggatttt ggtcatgaga ttatcaaaaa ggatcttcac  
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 5551 atgatggaaac ttgggtctgc agttaccaat gcttaatcag tgaggcacct  
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 5651 cgtgttagata actacgatac gggaggccg accatctggc cccagtcgt  
 5701 caatgatacc gcgagacca cgctcaccgg ctccagattt atcagcaata

FIGURE 16B

5751	aaccaggccag	ccggaaagggc	cgagcgcaga	agtggtcctg	caacttttac
5801	cgcctccatc	cagtctatta	attgttgccg	ggaagctaga	gtaagttagtt
5851	cggccagttaa	tagtttgcgc	aacgttggtg	ccattgctac	aggcatctgt
5901	gtgtcacgct	cgtcggttgg	tatggcttca	ttcagctccg	gttccccaaacg
5951	atcaaggcga	gttacatgat	cccccatgtt	gtgaaaaaaa	gcggtagtgc
6001	ccttcggtcc	tccgatcggt	gtcagaagta	agttggccgc	agtgttatca
6051	ctcatggtta	tggcagcact	gcataattct	cttactgtca	tgccatccgt
6101	aagatgtttt	tctgtgactg	gtgagttactc	aaccaagtca	ttctgagaat
6151	agtgtatgct	gcgaccgagt	tgctcttgc	cggtgtcaat	acgggataat
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6301	tgtaaaccac	tctgtgcaccc	aactgtatct	cagcatctt	tactttcacc
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6501	gaatgttattt	agaaaaataaa	acaaataggg	gttccgcgc	cattttcccg
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6751	gtgttggcgg	gtgtcggtt	tggcttaact	atgcggc	agagcagatt
6801	gtactgagag	tgcaccat	gccccgtgaa	ataccgcaca	gatgcgtaa
6851	gagaaaatac	cgcatcagga	aattgtaaac	gttaatattt	tgtaaaaatt
6901	cgcgttaat	tttgttaaa	tcagctcatt	ttttaaccaa	taggcccggaa
6951	tcggccaaaat	cccttataaa	tcaaaagaat	agaccgagat	agggttgagt
7001	gttgttccag	tttggaaacaa	gagttccacta	ttaaagaacg	tggactccaa
7051	cgtcaaaagg	cggaaaaaccg	tctatcaggg	cgatggccca	ctacgtgaac
7101	catcacccct	atcaagttt	ttgggggtcga	ggtgcgtaa	agcactaaat
7151	cggaaaccta	aaggggagccc	ccgatttaga	gcttgcgg	gaaagccggc
7201	gaacgtggc	agaaaaaggaa	ggaagaaaacg	gaaaggagcg	ggcgcttaggg
7251	cgctggcaag	ttagcggtc	acgtgcgc	taaccaccac	acccggccgc
7301	cttaatgcgc	cgttacagg	cgcgtcg	cattcgccat	tcaggctacg
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7401	ctgca				

FIGURE 16C

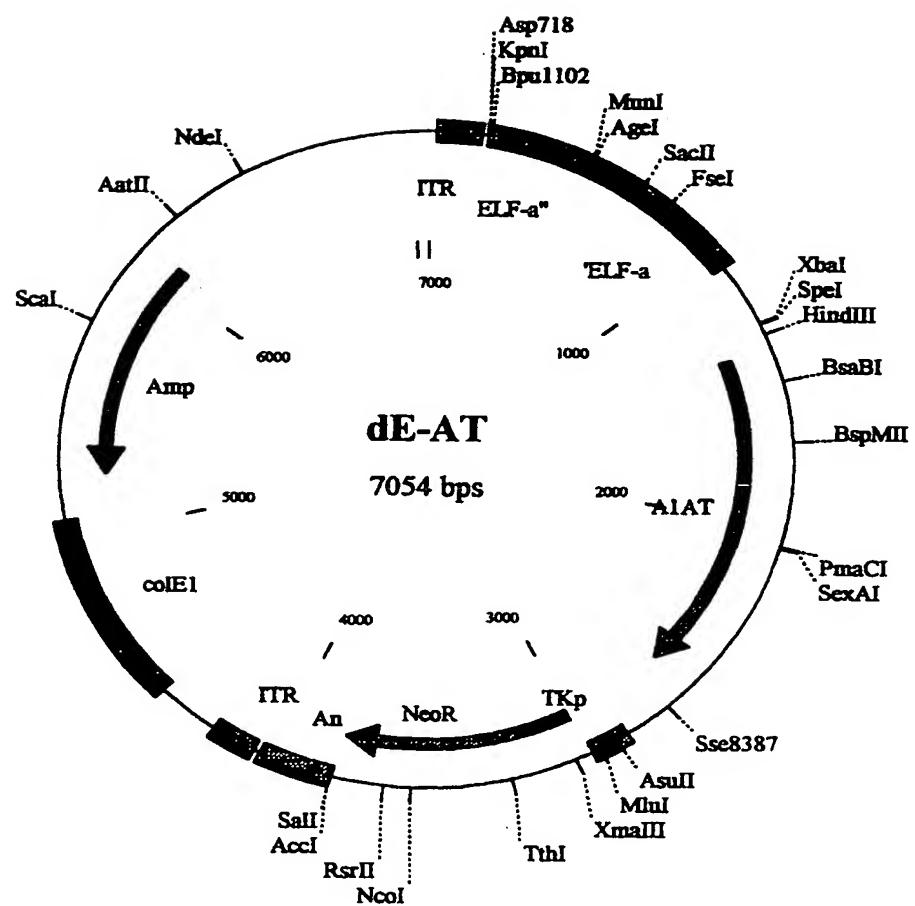


FIGURE 17

Molecule Name: dE-AT 25 / 59 7054 bps DNA Circular  
 Sequence Printed: 1-7054 (Full) Date Printed 16 Apr 1999  
 Description: Fragment 2 Circularized

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101 cggcctcagt gagcgagcga gcgcgcagag agggagtgcc caactccatc
151 actaggggtt cctagatctg aattcggtac ctggagacta agccagcaat
201 ggttagagggaa agattctgca cgcccttcc aggcggcctc cccgtcacca
251 ccccccccaa cccgccccga ccggagctga gagaattca tacaaaagga
301 ctgcggccctg ccttggggaa tcccagggac ctgcgttaaa ctcccaactaa
351 cgtagaaccc agagatcgct gctttccgc cccctcaccc gcccgtctc
401 gtcatcactg aggtggagaa gagcatgcgt gaggctccgg tgccgcgtcag
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751 gccaccgaga atcggacggg gtagtctca agctggccgg cctgcctctgg
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851 gcccggctgg caccagttgc gtgagccgaa agatggccgc ttcccgccccc
901 tgctgcaggg agctaaaaat ggaggacgcg ggcgtcgaa gagccggccg
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1001 tcatagtgact ccacggagta ccggggcccg tccaggcacc tcgattagtt
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1101 cgatggagggtt tccccacact gagtggtgg agactgaagt taggcagct
1151 tggcaacttga tgtaattctc ctggaaattt gccccttttgg agtttggatc
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1701 ctcagatcca tgaaggcttc caggaactcc tccgtacccct caaccagcca
1751 gacagccagc tccagctgac caccggcaat ggcctgttcc tcagcgaggg
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1851 cagaaggccct cactgtcaac ttccgggaca ccgaagaggc caagaaacag
1901 atcaacgatt acgtggagaa gggtaactaa gggaaaattt tggttgggt
1951 caaggagctt gacagagagaa cagtttttc tctggtaat tacatcttct
2001 ttaaaggcaa atggggagaga ccctttgaag tcaaggacac cgaggaagag
2051 gacttccacg tggaccaggt gaccaccgtg aagggtccctt tgatgaagcg
2101 tttaggcatt ttaacatcc agcactgtaa gaagctgtcc agctgggtgc
2151 tgctgatgaa atacctgggc aatgccaccg ccatcttctt cctgcctgat
2201 gaggggaaac tacagcacct gggaaatgaa ctcacccacg atatcatcac
2251 caagttccctg gaaaatgaag acagaaggctc tgccagctt cattaccca
2301 aactgtccat tactggAACC tatgatctga agagctcctt gggtaactg
2351 ggcacacta aggtcttcag caatggggct gacctctccg gggtcacaga
2401 ggaggcaccc ctgaagctct ccaaggccgt gcataaggct gtgtcgacca
2451 tcgacgagaa agggactgaa gctgtgggg ccatgtttt agaggccata
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FIGURE 17A

2751 aaaagcctct ccacccaggc ctggaatgtt tccacccaag tcgaaggcag  
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 2851 tttccaccca atgtcgagca acccccggca gcgctttgtc attggcgaat  
 2901 tcgaacacgc agatgcagtc gggggcggcgc ggtcccaggt ccacttcgca  
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 3001 atgggatcgg ccattgaaca agatggattg cacgcaggtt ctccggccgc  
 3051 ttgggtggag aggctattcg gctatgactg ggcacaaacag acaatcggt  
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 3701 agcttggcgg cgaatgggtc gaccgttcc tcgtgttta cggtatcgcc  
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 4851 ggccgtgtca cagagttctt gaagtgggtt cctaactacg gctacactag  
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 5351 aatgataccg cgagacccac gtcacccggc tccagattta tcagcaataa  
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 5651 cttcggtctt ccgatcggtt tcagaagttt gttggccgca gtgttatcac  
 5701 tcatggttat ggcagcactg cataattctc ttactgtcat gccatccgtt

FIGURE 17B

5751 agatgctttt ctgtgactgg tgagtactca accaagtcat tctgagaata  
5801 gtgtatgcgg cgaccgagtt gctctgccc ggcgtcaata cgggataata  
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5901 tcggggcgaa aactctcaag gatcttaccg ctgttgaagat ccagttcgat  
5951 gtaacccact cgtcaccca actgatcttc agcatcttt actttcacca  
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6151 aatgtattta gaaaaataaaa caaatagggg ttccgcgcac atttccccga  
6201 aaagtgcac ctgacgtcta agaaaccatt attatcatga cattaaccta  
6251 taaaaatagg cgtatcacga ggcccttgc tctcgcgcgt ttcggtgatg  
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6451 tactgagagt gcaccatatg cggtgtaaaa taccgcacag atgcgttaagg  
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6551 gcggttaaat ttgtttaaat cagtcattt ttaaccaat aggccgaaat  
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6701 gtcaaaggc gaaaaaccgt ctatcaggc gatggccac tacgtgaacc  
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6851 aacgtggcga gaaaggaaagg gaagaaagcg aaaggagcg ggcgttagggc  
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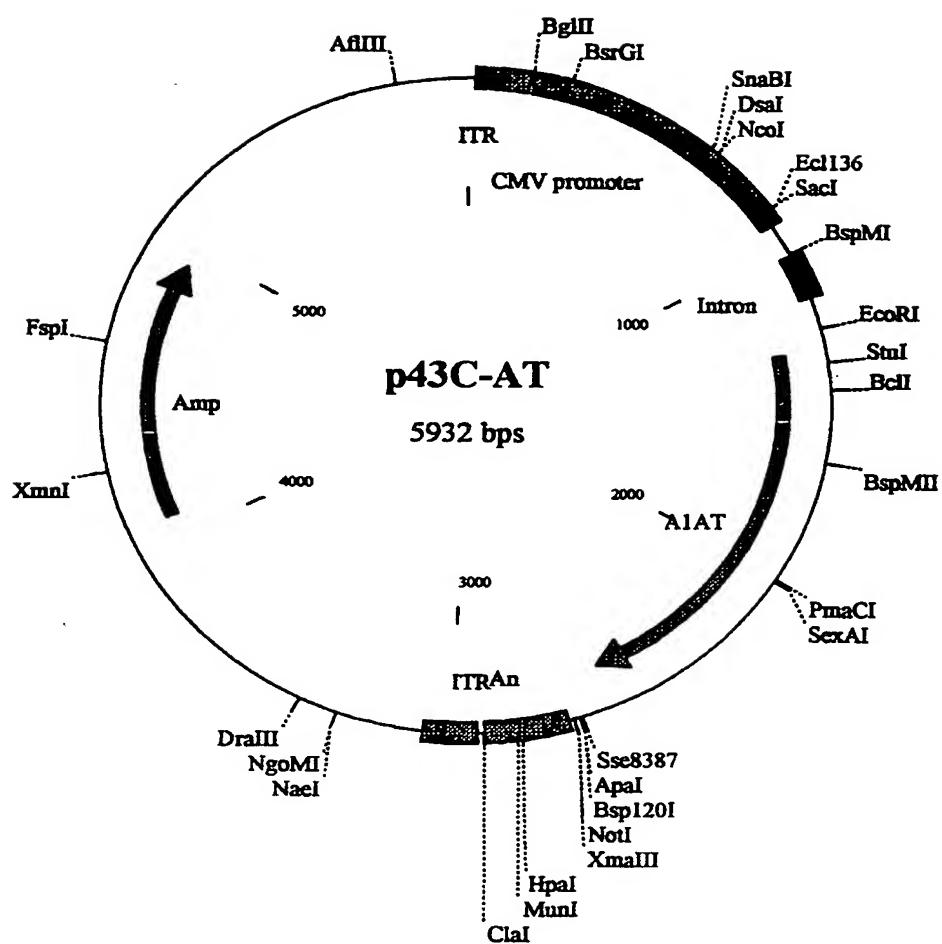


FIGURE 18

Molecule Name: p43C-AT 29 / 59 5932 bps DNA Circular  
 Sequence Printed: 1-5932 (Full) Date Printed 16 Apr 1999  
 Description: Ligation of TR and aat

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151 ctaggggttc ctagatcttc aatattggcc attagccata ttattcattg
201 gttatatacg ataaaatcaat attggctatt ggccatttgc tacgttgtat
251 ctatatacata atatgtacat ttatattggc tcatgtccaa tatgaccgcc
301 atgttggcat tgattattga cttagttatta atagtaatca attacgggt
351 cattagttca tagcccatat atggagttcc gcgttacata acttacggta
401 aatggccgc ctggctgacc gcccaacgac ccccgcccat tgacgtcaat
451 aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc
501 aatgggtgga gtatttacgg taaactgccc acttggcagt acatcaagtg
551 tatacatatgc caagtccgc ccctatttgc gtcaatgacg gtaaatggcc
601 cgcctggcat tattggccat acatgacctt acgggacttt cctacttggc
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701 cgtacacca atgggcgtgg atagcggtt gactcacggg gatttccaag
751 tctccaccccc attgacgtca atggagttt gtttggcact caaaatcaac
801 gggactttcc aaaatgtcgt aataaaaaaa cccctggac gcaaattggc
851 ggttaggcgtg tacgggtggaa ggtctatata agcagaggtc gtttagtcaa
901 ccgtcagatc actagaagct ttattgcgtt agtttatcac agttaaattt
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1101 gtttctgata ggcacctatt ggtcttactg acatccactt tgccttctc
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1951 cttaaaaggc aaatggggaga gaccctttga agtcaaggac accgagggaa
2001 aggacttcca cgtggaccac gtgaccaccc tgaagggtcc tatgtatgaag
2051 cgttttaggca tgtttaacat ccagcacgt aagaagctgt ccagctgggt
2101 gctgctgatg aaataacctgg gcaatggccac cgccatcttc ttctgcctg
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2551 gaatccacc caaaaataac tgcctctcgc tcctcaaccc ctcccccctcca
2601 tccctggccc cttccctggaa tgacattaaa gaagggttga gctggtaacc
2651 cccccccccc ctgcaggggc cctcgaccgg ggcggccgct tcgagcagac
2701 atgataagat acattgtatgaa gtttggacaa accacaacta gaatgcagt

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FIGURE 18A

30 / 59

2751 aaaaaaaatgc tttatgtg aaatttgta tgctattgct ttatgttaa  
 2801 ccattataag ctgcaataaa caagttacaaca acaacaattt cattcatttt  
 2851 atgttcagg ttcagggggg gatgtgggag gttttttaaa gcaagtaaaa  
 2901 cctctacaaa tgggttaaaa tcgataagga tcttaggaacc cctagtgtatg  
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FIGURE 18B

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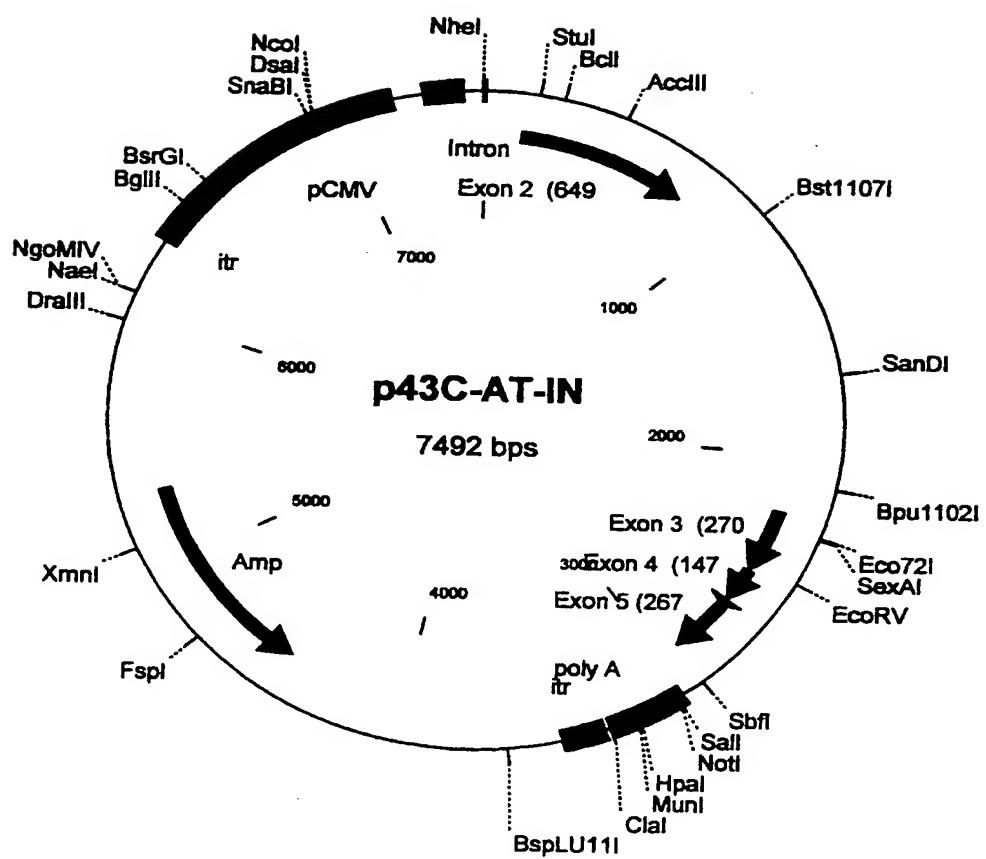


FIGURE 19

Molecule Name: p43C-AT-IN 7492 bps DNA Circular  
 Sequence Printed: 1-7492 (Full) Date Printed 16 Apr 1999  
 Description: Ligation of p43-C into IN

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151 gtctcgTggg gcatcctcct gctggcaggc ctgtgctGCC tggccctgt
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751 gttttgcTc tggtaattt catcttCTT aaaggtaagg ttgctcaacc
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FIGURE 19B

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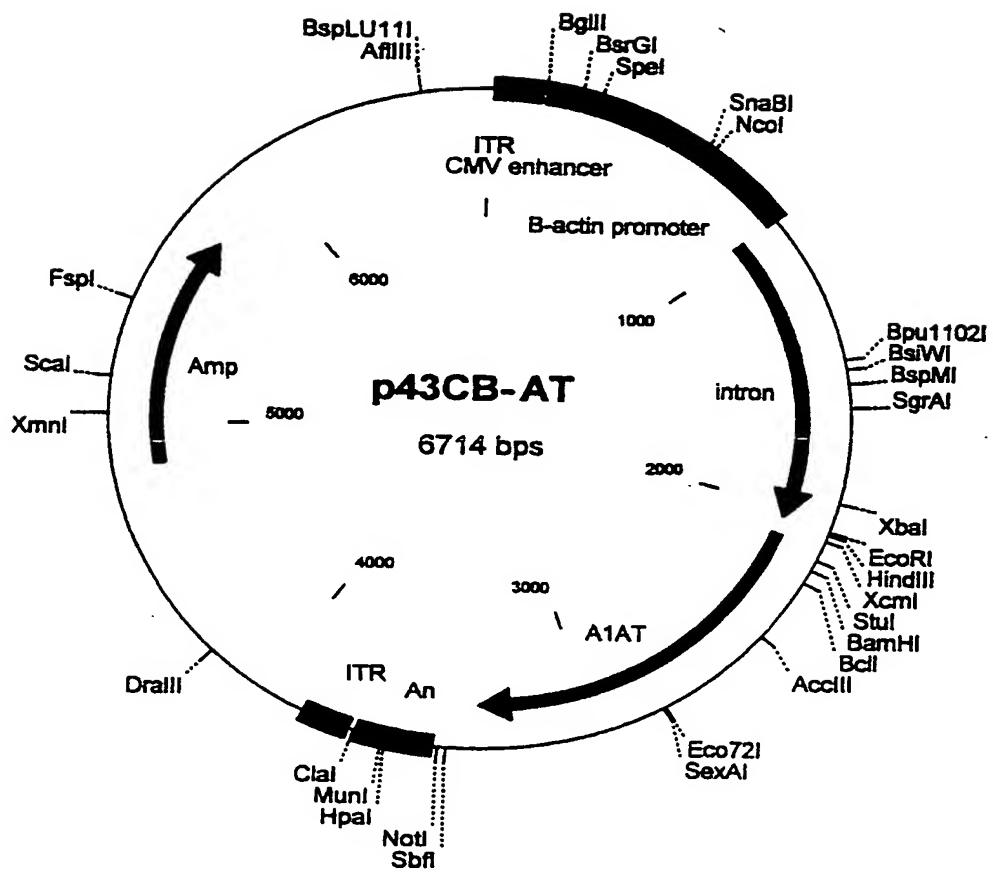


FIGURE 20

16 Apr 1999

## Sequence Data

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 Description: Ligation of Fragment 2 into Fragment 2  
 File Name: CB-AAT.cm5, dated 17 Nov 1998  
 Printed: 1-6714 bps (Full), format Single Strand

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2251    aacctggctg agttcgccctt cagccatac cgcggccgtt cacaccagtc
2301    caacagcacc aatatcttct tctcccccgtt gggatcgatc acagcccttg
2351    caatgctctc cctggggacc aaggctgaca ctcacgtatc aatcctggag
2401    ggcctgaatt tcaacctcac ggagattccg gaggctcaga tccatgaagg

```

FIGURE 20A

p43CB-AT

Page 2

2451 cttccaggaa ctccctccgt a ccctcaacca gccagacagc c agctccagc  
 2501 tgaccaccgg caatggcctg ttcctcagcg aggccctgaa gctagtggat  
 2551 aagtttttgg aggatgttaa aaagttgtac cactcagaag ccttcaactgt  
 2601 caacctcggg gacaccgaag aggccaagaa acagatcaac gattacgtgg  
 2651 agaagggtac tcaagggaaa attgtggatt tggtaagga gcttgacaga  
 2701 gacacagttt ttgctctggt gaattacatc ttctttaaag gcaa atgggaa  
 2751 gagaccctt gaa gtc aagg acaccgagga agaggacttc cacgtggacc  
 2801 aggtgaccac cgtgaagggtg cctatgatga a gcgtttagg catgtttaac  
 2851 atccagca ct gtaagaagct gtccagctgg gtgc tgc tga t gaaataac  
 2901 gggcaatgcc accgc catct tcttcc tgc tgatgagggg a aactacagc  
 2951 acctggaaaa tgaactcacc cacgatataca tcaccaagtt cctggaaaat  
 3001 gaagacagaa ggtctggccag cttacattt cccaaactgt ccattactgg  
 3051 aacccatgat ct gtaagagcg tcc tgggtca actgggcatc actaagg tct  
 3101 tcagcaatgg ggctgaccc tccgggg tca cagaggaggc acccc tgaag  
 3151 ctcttcaagg c cgtgcataa ggctgtgc accatcgacg agaaagg gac  
 3201 tgaagctgct gggccatgt ttttagaggc catacccatg tctatcccc  
 3251 ccgaggtcaa gttcaaca a cccttgc tcttaatgat tgaacaaaat  
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 3351 actgcctctc gtcctcaac ccctccccc catccctggc cccctccctg  
 3401 gatgacatta aagaagggtt gagctggtaa cccccccccc ccctgcagg  
 3451 gccc tgc acc cggcggccg ctgc gac gac a catgataag atacattgat  
 3501 gagtttggac aaaccacaac tagaatgcag tga aaaaat gcttattt  
 3551 t gaaattt gatgctattt gtttattt aaccattata agctgcaata  
 3601 aacaagttaa caacaacaat tgcattcatt ttatgttca gttcagg  
 3651 gagatgtggg aggttttta aagcaagtaa aacctctaca aatgtggtaa  
 3701 aatcgataag gatcttagaa ccccttagtga tggagg tggc cactccct  
 3751 ctgcgcgtc gtcgcgtcac tgaggccgc cggca aagc cggcgtcg  
 3801 ggcacccctt ggtgc cccgg cctc agt gtag cgacg cgc a gagg  
 3851 gagttgcca a cccccccccc ccccccctg cagc tggc taatgcga  
 3901 gaggcccgca ccgatcgccc ttcccaac ag ttgc ttagcc tgaatggcga  
 3951 atggcgcgac ggc ccc tga gggcgcatt a a g c g c g c g g t g t  
 4001 ttacgcgcag cgtgaccgct acacttgc a g c g c c t a g c g c  
 4051 ttgc tttct tcccttcc ttcgc acg ttcgcggc t t c c c g t c a  
 4101 agctctaaat cggggctcc ct taggggtt ccgatttagt gcttacggc  
 4151 acctcgaccc caaaaactt gattagggtt atggttacg tagtggcca  
 4201 tcgcctgat agacggttt tcgc ctttgc acgttggagt ccacgttctt  
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 4401 aacgttaca atttctgat g c g g t t t t c t c t a c g a t c g g  
 4451 tatttacac c g c a t a t g g t g c a t c t c a g t a a t c t g c  
 4501 catagttaa c c a g c c c g a c a c c c g c c a a c a c c c g t g a  
 4551 cgggcttgc tgctcccgcc atccgcttac agacaagctg tgaccgtctc  
 4601 cgggagctgc atgtgtcaga ggttttacc g t c a t c a c c g a a a c g c g c g a  
 4651 gacgaaaggc cctcgtgata cgcctatttt tata gttt a a t g t c a t g a t a  
 4701 ataatggttt cttagacg t c a g t g g c a c t t t t c g g g g a a t g t g c g c g g  
 4751 aaccctatt t g t t t a t t t t t c t a a a t a c a t t c a a t a t g t a t c c g c t c a  
 4801 tgagacaata accctgataa atgcttcaat aatattgaaa a a g g a a g a g t  
 4851 atgagttt aacattccg t g t c g c c c t t a t t c c t t t t t t t g c g g c a t t  
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 4951 ctgaagatca gttgggtgca cgagttgggtt acatcgact g g a t c t c a a c  
 5001 agcgttaaga tccttggag tttcgc cccca g a a g a c g t t t c c a a t g a t g a t  
 5051 gagcactttt a a g t t c t g c t a g t g g c g c g t t a t t a t c c g t a t t g a c g  
 5101 ccggcaga a g c a a c t c g g t c g c c g c a t a c a c t a t t c t c a a g t g a c t t g  
 5151 gttgagtttactt caccagtcac agaaaagcat cttacggat gcatgacag

FIGURE 20B

p43CB-AT

Page 3

5201 aagagaatta tgcagtgctg ccataaccat gagtgataac actgcggcca  
5251 acttacttct gacaacgatc ggaggaccga aggagctaac cgctttttg  
5301 cacaacatgg gggatcatgt aactcgccct gatcgttggg aaccggagct  
5351 gaatgaagcc ataccaaacg acgagcgtga caccacgatg cctgttagcaa  
5401 tggcaacaac gttgcgcaaa ctattaactg gcgaactact tactctagct  
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5601 ggtaaggccct cccgtatcgt agttatctac acgacgggga gtcaggcaac  
5651 tatggatgaa cgaaatagac agatcgctga gataagggcc tcactgatta  
5701 agcattggta actgtcagac caagtttact catatatact ttagattgat  
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5801 taatctcatg accaaaatcc cttaacgtga gtttgcgtt cactgagcgt  
5851 cagacccccgt agaaaaagatc aaaggatctt cttgagatcc ttttttctg  
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5951 ttgttgcgg gatcaagagc taccaactct tttccgaag gtaactggct  
6001 tcagcagagc gcagatacc aataactgtcc ttctagtgtt gccgtatgtt  
6051 ggccaccact tcaagaactc tgttagcaccg cctacatacc tcgctctgct  
6101 aatccctgtta ccagtggctg ctgcccagtgg cgataagtgc tgcttaccg  
6151 ggttggactc aagacgatag ttaccggata aggcgcagcg gtcgggctga  
6201 acgggggggtt cgtgcacaca gcccagctt gaggcaacga cctacaccga  
6251 actgagatac ctacagcgtg agcattgaga aagcgccacg cttcccaag  
6301 ggagaaaaggc ggacaggtat ccggtaagcg gcagggtcg aacaggagag  
6351 cgcacgaggg agcttccagg gggaaaacgccc tggtatctt atagtcctgt  
6401 cgggttcgc cacctctgac ttgagcgtcg attttgtga tgctcgtcag  
6451 gggggcggag cctatggaaa aacgcccagca acgcggccctt tttacggttc  
6501 ctggcccttt gctggccctt tgctcacatg ttctttctg cgttatcccc  
6551 tgattctgtg gataaccgta ttaccgcctt tgagtgagct gataaccgctc  
6601 gcccgagccg aacgaccgag cgagcgtgat cagtgagcga ggaagcggaa  
6651 gagcgcccaa tacgcaaaacc gcctctcccc gcgcgttggc cgattcatta  
6701 atgcaggcgt gcag

FIGURE 20C

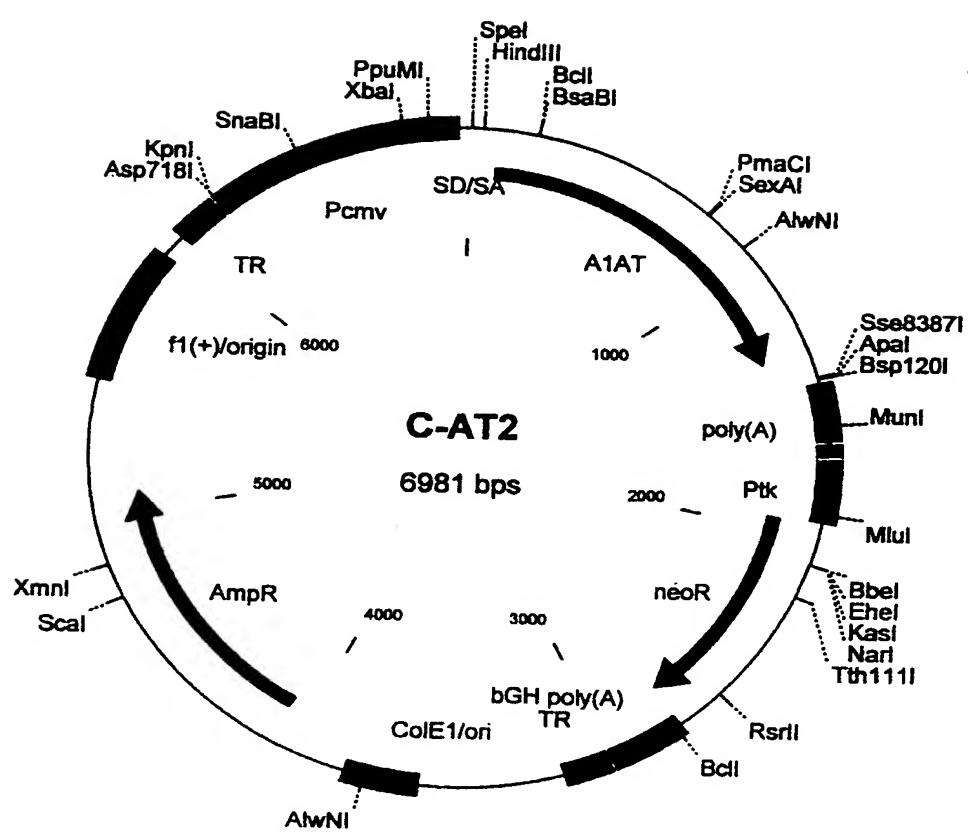


FIGURE 21

Molecule Name: C-AT2 6981 bps DNA Circular  
 Sequence Printed: 1-6981 (Full) Date Printed 16 Apr 1999  
 Description: Ligation of Fragment 1 and Fragment 2

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101  ttctgtctcg tggggcatcc tcctgtggc aggccctgtgc tgcttggtcc
151  ctgtctccct ggctgaggat cccccagggag atgctgcca gaagacagat
201  acatcccacc atgatcagga tcacccaacc ttcaacaaga tcaccccaa
251  cctggctgag ttgccttca gcctataaccg ccagctgca caccagtcca
301  acagcaccaa tatcttcttc tccccagtga gcatcgctac agcctttgca
351  atgctctccc tggggaccaa ggctgacact cacgatgaaa tcctggaggg
401  cctgaatttc aacccacgg agattccgga ggctcagatc catgaaggct
451  tccaggaact cctccgtacc ctcaaccagc cagacagcca gctccagctg
501  accaccggca atggcctgtt cctcagcgag ggcctgaagc tagtggataa
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601  acttcgggga caccgaagag gccaagaaac agatcaacga ttacgtggag
651  aagggtactc aaggaaaaat tgtggatttgc tcaaggagc ttgacagaga
701  cacagtttt gctctgtgtca attacatctt ctttaaaggc aaatgggaga
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801  gtgaccacgg tgaagggtgcc tatgtgaag cgtttagca tggttaacat
851  ccagcactgt aagaagctgt ccagctgggt gctgctgtatc aaatacctgg
901  gcaatgccac cgccatcttc ttccctgc ttaggggaa actacagcac
951  ctggaaaatg aactcaccaa cgatatcatc accaagtccc tgaaaatga
1001  agacagaagg tctgcccgtct tacatttacc caaactgtcc attactggaa
1051  cctatgatct gaagagcgcc ctgggtcaac tgggcattcac taaggtcttc
1101  agcaatgggg ctgacccctc cggggtcaca gaggaggccac ccctgaagct
1151  ctccaaggcc gtcataagg ctgtgtgcac catcgacgag aaaggactg
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1251  gaggtcaagt tcaacaaaacc ctttgttcc ttaatgatttgc aacaaaataac
1301  caagtctccc ctcttcatgg gaaaagtggt gaatcccacc caaaaataaac
1351  tgcctctcgc tcccaacccc ctccctccca tccctggccc cctccctggaa
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1751  gtgggtttgc aagaggaagc aaaaagccctc tccacccagg cctggaatgt
1801  ttccacccaa tgcgagcaa ccccccagg cgtttgtca ttggcgaatt
1851  cgaacacgca gatgcagtcg gggcggcgcg gtcccagtc cacttcgcatt
1901  attaagggtga cgcgtgtggc ctcgaacacc gagcgcacct gcagccaata
1951  tgggatcgcc cattgaacaa gatggattgc acgcagggttcc tccggccgct
2001  tgggtggaga ggctattcgg ctatgactgg gcacaacaga caatcggtcg
2051  ctctgtatgcc gccgtgttcc ggctgtcagc gcagggggcgc cgggttctt
2101  ttgtcaagac cgacctgtcc ggtgcctga atgaactgca ggacgaggca
2151  gcgccgctat cgtggctggc caccgcggc gtcccttgcg cagctgtgtc
2201  cgacgttgc actgaagcgg gaaggactg gctgttatttgc ggcgaagtgc
2251  cggggcagga tctcctgtca ttcaccccttgc tccctgcggaa gaaagtatcc
2301  atcatggctg atgcaatgcg gcggtgcatttgc acgcttgatc cggctacctg
2351  cccattcgcac caccacggc aacatcgatc cgagcggca cgtactcgaa
2401  tggaaagccgg tcttgcgtat caggatgtatc tggacgaaaga gcatcagggg
2451  ctcgcgcac ccgaactgtt cgcgcggc aaggcgcgc tgcggcgcgg
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2651  gcttggcggc gaatgggctg accgccttcc cgtgtttac ggtatcgccg
2701  ctcccgatcc gcagcgcatttgc gccttctatc gccttcttgc cgagttcttc

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FIGURE 21A

42 / 59

2751 tgaggggatc cgtcgactag agctcgctga tcagcctcga ctgtgccttc  
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 3451 tcgacgctca agtcagagg ggcgaaaaccc gacaggacta taaagataacc  
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 4751 tggatgcggc gaccgagttt ctcttgcggc gctcaatac gggataata  
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 5651 tcaaaggcg aaaaaccgtc tatcaggggcg atggccact acgtgaacca  
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FIGURE 21B

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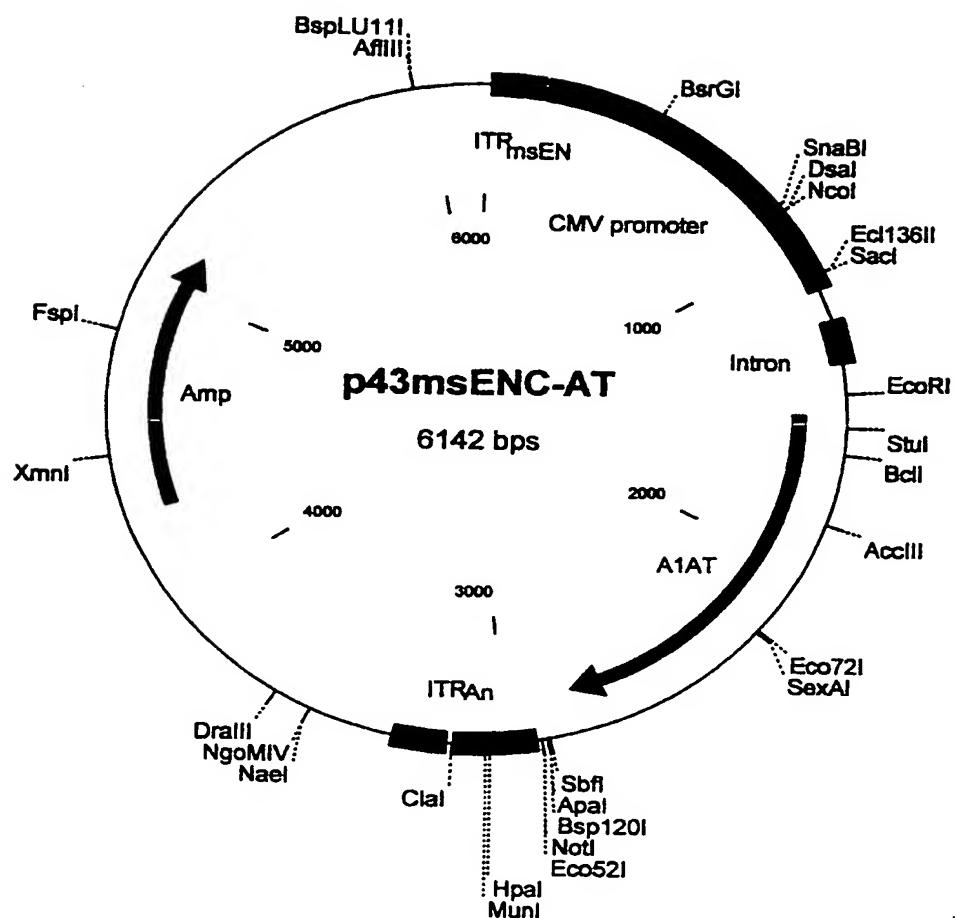


FIGURE 22

19 Apr 1999

## Sequence Data

Page 1

Molecule: p43msENC-AT, 6142 bps DNA Circular  
 Description: Ligation of inverted msEnhancer into p43-AAT\*  
 File Name: p43smENC-AT.cm5, dated 19 Apr 1999  
 Printed: 1-6142 bps (Full), format Single Strand

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601    acttacggta aatggcccgcc ctggctgacc gccaacgac ccccgcccat
651    tgacgtcaat aatgacgtat gttcccatag taacgccaat agggacttcc
701    cattgacgtc aatgggtgga gtatttacgg taaactgccc acttggcagt
751    acatcaaagt tatcatatgc caagtccgc ccctatttgc gcataatgacg
801    gtaaatggcc cgcctggcat tatgcccagt acatgacctt acgggacttt
851    cctacttggc agtacatcta cgtatttagtc atcgcttata ccatggtgat
901    gcggtttgg cagttacacca atggggctgg atagcggtt gactcacggg
951    gatttccaag tctccacccatttgcgtca atgggagttt gttttggcac
1001   caaaatcaac gggactttcc aaaatgtcgt aataaaccgg ccccggttgc
1051   gcaaattggc ggtaggcggtg tacgggtggaa ggtcttatata agcagagctc
1101   gtttagtgaa ccgtcagatc actagaagct ttattgcgtt agtttatcac
1151   agttaaatttgc ttaacgcgtt cagtgcatttgc gacacaacag tctcaactt
1201   aagctgcaga agttggcgtt gaggcactgg gcaggttaatg atcaaggta
1251   caagacaggta ttaaggagac caatagaaac tggcttgatc gagacagaga
1301   agactcttgc gtttctgata ggcacctatt ggtcttactg acatccactt
1351   tgcctttctc tccacagggtt tccactccca gttcaattac agctcttaag
1401   gctagagttac ttaatacgcac tcactatagg ctagaacttag tggatcccc
1451   gggctgcagg aattcgatata caagcttggg gattttcagg caccaccact
1501   gacctggggc agtgaatcga caatgccgtc ttctgtctcg tggggcatcc
1551   tcctgtggc aggctgtgc tgctgggtcc ctgtctccct ggctgaggat
1601   ccccaaggggat agtgcgttca gaagacagat acatcccacc atgatcagga
1651   tcacccaacc ttcaacaaga tcaccccaaa cctggcttag ttcgccttca
1701   gcctataccg ccagctggca caccagtccca acagcaccaa tatctttttc
1751   tccccagtga gcatcgctac agcctttgcata atgctctccc tggggaccaa
1801   ggctgacact cacgatgaaa tcctggagggg cctgaatttc aacctcacgg
1851   agattccggaa ggctcagatc catgaaggct tccaggaact cctccgtacc
1901   ctcaaccaggc cagacagcca gctccagctg accaccggca atggcctgtt
1951   cctcagcgag ggcctgaagc tagtggataaa gttttggag gatgttaaaa
2001   agttgtacca ctcagaagcc ttcaactgtca acttcggggaa caccgaagag
2051   gccaagaaac agatcaacga ttacgtggag aagggtactc aaggaaaaat
2101   tgtggatttgc gtcaaggagc ttgacagaga cacagtttt gctctgggtga
2151   attacatctt ctttaaaggc aaatggggaga gaccctttga agtcaaggac
2201   accggaggaag aggactttca cgtggaccag gtgaccaccg tgaaggtgcc
2251   tatgtatggaa cgtttaggca tggtaaacat ccagcaactgt aagaagctgt
2301   ccagctgggt gctgctgtatc aaatacctgg gcaatgccac cgccatcttc
2351   ttcctgccttgc atgaggggaa actacagcac ctggaaaatg aactcacccca
2401   cgatatcatac accaagtcc tggaaaatga agacagaagg tctgcacagct

```

FIGURE 22A

p43msENC-AT

Page 2

2451 tacatttacc caaactgtcc attactggaa cctatgatct gaagagcgtc  
 2501 ctgggtcaac tgggcacatc taaggtctt agcaatgggg ctgacctctc  
 2551 cggggtcaca gaggaggcac ccctgaagct ctccaaggcc gtgcataagg  
 2601 ctgtgctgac catcgacgag aaagggactg aagctgctgg ggccatgttt  
 2651 ttagaggcca tacccatgtc tatccccccc gaggtcaagt tcaacaaacc  
 2701 ctttgtctt ttaatgattt aaaaaataac caagtctccc ctcttcatgg  
 2751 gaaaagtggt gaatcccacc caaaaataac tgctctcgc tcctcaaccc  
 2801 ctcccctcca tccctggccc cctccctggta tgacattaaa gaagggttga  
 2851 gctggtaacc ccccccccccc ctgcaggggc cctcgacccgg ggcggccgct  
 2901 tcgagcagac atgataagat acattgtga gtttgacaa accacaacta  
 2951 gaatgcagtg aaaaaaatgc tttatTTTGTG aaatttgtga tgctattgct  
 3001 ttatttgtaa ccattataag ctgcaataaa caagtttaaca acaacaattg  
 3051 cattcatttt atgtttcagg ttcaggggaa gatgtgggag gtttttaaa  
 3101 gcaagtaaaa cctctacaaa tgtggtaaaa tcgataagga tctaggaacc  
 3151 cctagtgtat gagttggcca ctccctctt gcgcgctcgc tcgctactg  
 3201 aggccgccccg ggcaaagccc gggcgtcggg cgacctttgg tcgccccggcc  
 3251 tcagtgagcg agcgagcgcg cagagagggaa gtggcaacc ccccccccccc  
 3301 ccccccgtca gcctggcgta atagcgaaga ggcccgcacc gatcgccctt  
 3351 cccaaacagg tgcgtggcctg aatggcgaat ggccgcacgc gcccctgttagc  
 3401 ggcgcattaa ggcgcggcggg tgtgggtggtt acgcgcagcg tgaccgctac  
 3451 acttgcgcgc gcccttagcgc cgcctccctt cgctttcttc cttcccttcc  
 3501 tcgcacgtt cgccgggtt ccccgtaag ctctaaatcg ggggctccct  
 3551 ttagggttcc gatttagtgc ttacggcac ctgcacccca aaaaacttga  
 3601 ttagggtgat gttcacgtt gttggggccat gcccgtatag acggtttttc  
 3651 gccccttgac gttggagtcc acgttctttt atagtgact cttgttccaa  
 3701 actgaaacaa cactcaaccc tatctcggtc tattttttt atttataagg  
 3751 gatttgccg atttcggcct attggtaaaa aaatgagctg atttaacaaa  
 3801 aatttaacgc gaatttttaac aaaatattaa cgtttacaat ttctgtatgc  
 3851 ggtatTTTCT ctttacgtt ctgtgcggta tttcacaccg catatggtgc  
 3901 actctcagta caatctgttc tgatgccgca tagtaagcc agcccccaca  
 3951 cccgccaaca cccgctgacg cgcctgacg ggcttgcctg ctcccccgcatt  
 4001 ccgcttacag acaagctgtg accgtctccg ggagctgcatt gtgtcagagg  
 4051 ttTtaccgtt catcacccaa acgcgcgaga cgaaggggcc tcgtgatacgt  
 4101 cctatttttta taggttaatg tcatgataat aatggttct tagacgtcag  
 4151 gtggcactt tcggggaaat gtgcgcggaa cccctatttgc tttatTTTTC  
 4201 taaatacatt caaatatgtt tccgcctcatg agacaataac cctgataaaat  
 4251 gcttcaataa tattgaaaaaa ggaagagtat gagtattcaa cattttccgtg  
 4301 tcgccttat tccctttttt gcggcattttt gccttctgt ttttgcac  
 4351 ccagaaacgc tggtaaaatg aaaagatgtt gaagatcagt tgggtgcacg  
 4401 agtgggttac atcgaactgg atctcaacag cggtaagatc cttgagagtt  
 4451 ttccgcggca agaacgtttt ccaatgtatc gcaactttaa agttctgtta  
 4501 tggcgcggg tattatccc tattgacgcc gggcaagagc aactcggtcg  
 4551 ccgcatacac tattctcaga atgacttgg tgagtactca ccagtacac  
 4601 aaaagcatct tacggatggc atgacagtta gagaattatg cagtgcgtcc  
 4651 ataaccatgtt gtgataacac tgcggccaaat ttacttctgtt caacgatcg  
 4701 aggaccgaag gagctaaccg ctttttgc tcaacatgggg gatcatgtaa  
 4751 ctcgccttgc tcgttggaa ccggagctgtt atgaagccat accaaacgc  
 4801 gagcgtgaca ccacgtgcc tgtagcaatg gcaacaacgt tgcgcacact  
 4851 attaactggc gaactactt ctctagctt ccggcaacaa ttaatagact  
 4901 ggatggaggc ggataaaatgtt gcaaggaccat ttctgcgtcc ggccttccg  
 4951 gctggctgtt ttattgtgtt taaatctgtt gccgggtgacg tgggtctcg  
 5001 cggtatcatt gcaacactgg ggccagatgg taagccctcc cgtatcgtag  
 5051 ttatctacac gacggggagt caggcaacta tggatgaacg aaatagacag  
 5101 atcgctgaga taggtgcctc actgattaag cattggtaac tgcagacca  
 5151 agtttactca tataactttt agattgatt aaaacttcat ttttattta

FIGURE 22B

p43msENC-AT

Page 3

5201 aaaggatcta ggtgaagatc ctttttgata atctcatgac caaaatccct  
5251 taacgtgagt tttcggttcca ctgagcgtca gaccggtag aaaaatcaa  
5301 aggatcttct tgagatcctt ttttctgcg cgtaatctgc tgcttcaaa  
5351 caaaaaaacc accgctacca gcgggtggtt gtttgcggta tcaagagcta  
5401 ccaactcttt ttccgaaggt aactggcttc agcagagcgc agataccaaa  
5451 tactgtcctt ctagtgttagc ctaggttagg ccaccacttc aagaactctg  
5501 tagcaccgcc tacatacaccc gctctgctaa tcctgttacc agtggctgct  
5551 gccagtggcg ataagtcgtg tcttaccggg ttggactcaa gacgatagtt  
5601 accggataag gcgcagccgt cggtgtgaac ggggggttcg tgcacacagc  
5651 ccagcgttggc gcgaacgacc tacaccgaac tgagataacct acagcgtgag  
5701 cattgagaaa gcggccacgt tcccgaaagg agaaaaggcgg acaggtatcc  
5751 ggtaagcggc agggtcgaa caggagagcg cacgagggag cttccagggg  
5801 gaaacgcctg gtatctttat agtccgttcg ggttcgcca cctctgactt  
5851 gagcgtcgat ttttgtgtatc ctcgtcaggg gggccggagcc tatggaaaaaa  
5901 cggccagcaac gcggcccttt tacgggttcctt ggcctttgc tggcctttg  
5951 ctcacatgtt ctttcctgcg ttatcccctg attctgttggta taaccgtatt  
6001 accgccttg agtgagctga taccgctcgc cgcaagccgaa cgaccgagcg  
6051 cagcgagtca gtgagcggagg aagcggaaaga gcgcggaaata cgcaaaaccgc  
6101 ctctccccgc gcgttggccg attcattaat gcagggctgc ag

FIGURE 22C

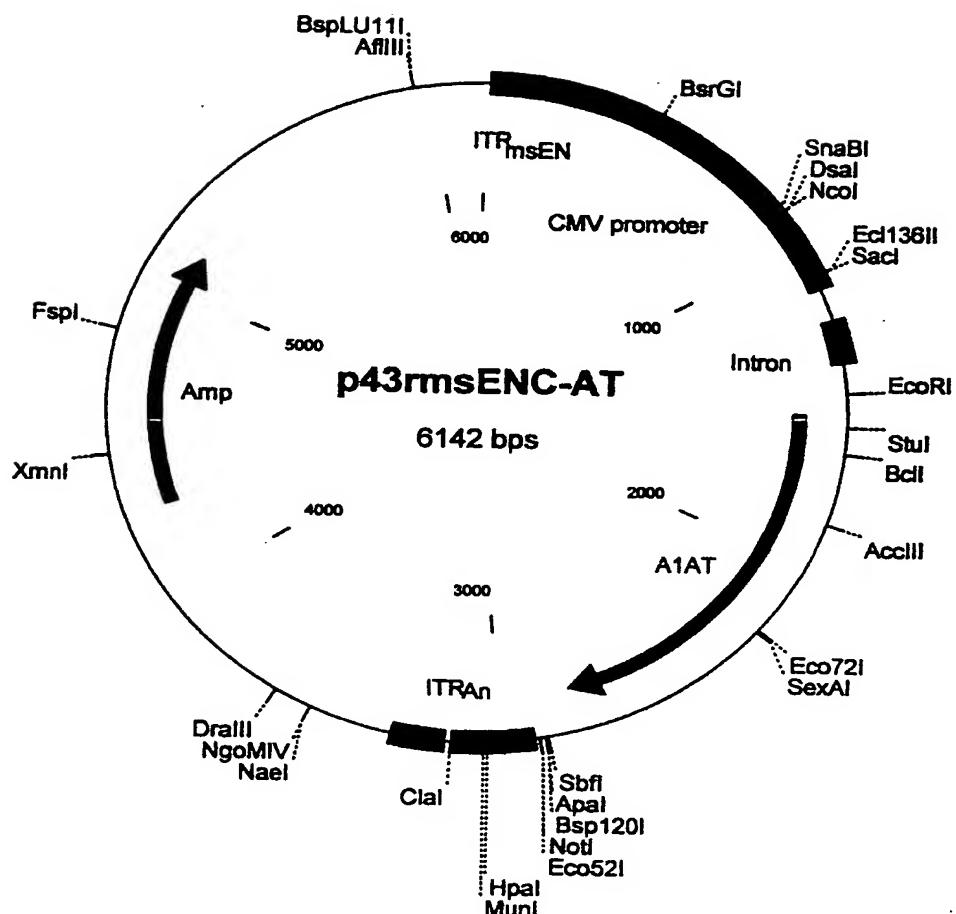


FIGURE 23

19 Apr 1999

## Sequence Data

Page 1

Molecule: p43rmsENC-AT, 6142 bps DNA Circular  
 Description: Ligation of inverted msEnhancer into p43-AAT\*  
 File Name: p43rmsENC-AT.cm5, dated 19 Apr 1999  
 Printed: 1-6142 bps (Full), format Single Strand

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1      gggggggggg ggggggggttgc cccactccct ctctgcgcgc tcgctcgctc
51     actgaggccg ggcgaccaaa ggtcgccccga cgccccggc ttgcccggc
101    ggccctcagtgc agcgagcgag cgccgcagaga gggagtgcc aactccatca
151    ctaggggttc ctagatctga cacccaaata tggctctgggg tgaggaatgg
201    tgccgtcgcc atattttgggt gtccaccatt cctcaccgcct ctaaaaataaa
251    ctccccggag ttattttttag agcgccaaca cctgtgcct gccaccatt
301    cctcaccgcct ctaaaaataaa ctccccacca ttcttcaccc gtcgcacat
351    ttgggtgtcg tgaggaatgg tgagatctc aatattggcc attagccata
401    ttatttcatttgc gttatatacg ataaatcaat attggcttattt ggccattgc
451    tacgttgtat ctatatacata atatgtacat ttatattggc tcatgtccaa
501    tatgaccgcct atgttgcatt tgattattga ctatgttatta atagaatca
551    attacggggcattatgttca tagcccatat atggagttcc gcgttacata
601    acttacggta aatggccgcg ctggctgacc gccaacgcac ccccgcccat
651    tgacgtcaat aatgacgtat gttcccatag taacgccaat agggactttc
701    cattgacgtc aatgggttgcgttacgg taaactgcctt acttggcagt
751    acatcaagtgc tatcatatgc caagtccgc ccctatttgcgtcaatgc
801    gtaaatggcc cgcctggcat tatgcccagt acatgacctt acgggacttt
851    cctacttggc agtacatcta cgtttagtc atcgcttata ccatgtgtat
901    gcggtttgg cagtagacca atgggcgtgg atagcggtt gactcacggg
951    gatttccaag tctccacccatgcattacgcgttacggatggagttt gttttggcac
1001   caaaatcaac gggactttcc aaaatgtcgt aataaaccgg ccccggttgc
1051   gcaaatgggc ggttaggcgtg tacgggtggga ggtctatata agcagagctc
1101   gtttagtgaatccgtcagatc actagaagct ttatttgcgtt agtttatcac
1151   agttaaatttgc taaacgcgtt cagtgcctt gacacaacag tctcaactt
1201   aagctgcaga agttggcgtt gaggcacttgg gcaggtaagt atcaaggta
1251   caagacaggt ttaaggagac caatagaaac tggcttgcgtt gagacagaga
1301   agactcttgc gtttctgtata ggcacctt ggtcttactt acatccactt
1351   tgcctttctc tccacagggtt tccactccca gttcaatttac agctcttaag
1401   gcttagagtttcaatatacgac tcactatagg ctagaacttgc tggatcccc
1451   gggctgcagg aattcgatataatcaagcttggg gattttcagg caccaccact
1501   gacctgggac agtgaatcgatcaatggccgttcc ttctgtctcg tggggcatcc
1551   tcctgctggc aggccctgtgc tggcttgcgttcc ctgtctccct ggctgaggat
1601   ccccaaggag atgtgcgttca gaagacatgc acatcccacc atgtatcgga
1651   tcacccaacc ttcaacaaga tcaccccaaa cctggcttgc ttcgccttca
1701   gcctataccg ccagctggca caccaggccca acagcacca tatcttcttc
1751   tccccaggatgcatcgcttcc accctttgcataatgccttcc tggggaccaa
1801   ggctgacact cacgtgaaaa tcctggagggtt cctgaatttca aacccacgg
1851   agattccggaa ggctcagatc catgaaggcttccaggactt cctccgttacc
1901   ctcaaccaggc cagacagggca gctccagctt accaccggca atggccgttt
1951   cctcagcgag ggcctgaagc tagtggataa gtttttggag gatgttaaaaa
2001   agttgtacca ctcagaagcc ttcaactgtca acttcggggaa caccgaagag
2051   gccaagaaac agatcaacgc ttacgtggag aagggtactt aaggaaaat
2101   tgtggatttgc tcaaggagc ttgacagaga cacagttttt gctctggcgtt
2151   attacatctt cttaaaaggc aaatgggaga gacccttgc agtcaaggac
2201   accgagggaaag aggacttccatgcgtggaccatgcgttggaccacccg tgaagggttcc
2251   tatgtatggatgc tggatggcgttggaccatgcgttggaccacccg tgaagggttcc
2301   ccagctgggt gctgctgtatgc tggatggcgttggaccatgcgttggaccacccg tgaagggttcc
2351   ttccctgccttgc atgaggggaa actacagcaccatgcgttggaccatgcgttggaccacccg tgaagggttcc
2401   cgatatcatc accaaggatcc tggaaaatgc tggaccatgcgttggaccacccg tgaagggttcc

```

FIGURE 23A

p43rmsENC-AT

Page 2

2451 tacatTTacc caaaactgtcc attactggaa cctatgatct gaagagcgTC  
 2501 ctgggtcaac tgggcacTcac taaggTcttc agcaatgggg ctgacctCTC  
 2551 cggggTcaca gaggaggcac ccctgaagct ctccaaggCC gtgcataagg  
 2601 ctgtgTgcac catcgacgag aaagggaCTg aagctgctgg ggccatgttt  
 2651 tttagggCCA taccatgtc tatccccccc gaggtcaagt tcaacaaacc  
 2701 ctttgtCTTC ttaatgattg aacaaaatac caagtCTCCC ctcttcatgg  
 2751 gaaaagtggt gaatcccacc caaaaataac tgcctCTCGC tcctcaacCC  
 2801 ctcccTCCA tccctgccc cctccCTgA tgacattaaa gaagggttga  
 2851 gctggtaacc cccccccccctg ctcgaggGGC cctcgacCCG ggcggccgct  
 2901 tcgagcagac atgataagat acattgatGA gtttggacAA accacaacta  
 2951 gaatgcagtG aaaaaaatGC ttTATTtGtG aaatttGtGA tgctattGt  
 3001 ttatttGtaa ccattataAG ctgcaataaa caagttaca acaacaattG  
 3051 cattcatttt atgtttcagg ttcaGGGGGA gatgtgggag gttttttaaa  
 3101 gcaagtaaaa cctctacaaa tgggttaaaa tcgataaggA tcttaggaacc  
 3151 cctagtgtG gagttggCCA ctccCTCTC gcgcgCTCGC tcgctcaCTG  
 3201 aggcccccGG ggcaaAGccc gggcgtcGGG cgacCTTGG tcgcccggCC  
 3251 tcagtgagcg agcgagcgcg cagagaggGA gtggccaacc ccccccccc  
 3301 cccccCTgCA gcctggcgTA atagcgaaga ggcccgacCC gatgcCcCtt  
 3351 cccaaCAGtt gcgttagcCTG aatggcgaat ggcgcgacgc gCcCtGtAgC  
 3401 ggCgcattAa ggcggggGGG tgggtgggtt acgcgcagcg tgaccgctac  
 3451 acttggcagc gCcCTagcgc ccgctcCtt cgcttCttc cttccCttc  
 3501 tcGCCAcgtt cggccggCttt ccccgtaaCg ctctaaatCg ggggCtCcCt  
 3551 ttagggttcc gatttagtGc ttacggcac ctgcacCCCA aaaaacttga  
 3601 ttagggtgat ggTcacgtA gttggccatC gcCcTgtatAG acggtttttc  
 3651 gCcCtttgac gttggagtc acgttCttt atagtggact Cttgttccaa  
 3701 actggaaCaa cactcaacCC tatctcggtc tatttttttG atttataagg  
 3751 gatttgccG atttcgGcCt atgggttaaa aaatgagctG atttaacaaa  
 3801 aatttaacgc gaatttttaac aaaatattaa cgttacaat ttctgtatGc  
 3851 ggtattttct cttacgcAt ctgtgcggta tttcacacCG catatgtGc  
 3901 actctcagta caatctgctc tgatGCCGA tagttaaGcc agccccgaca  
 3951 cccgccaaca cccgctgacG cggcctgacG ggcttgctG ctcccgcat  
 4001 ccgcttacag acaagctgtG accgtctccG ggagctgcat gtgtcagagg  
 4051 ttttCaccGT catcacccGA acgcgcgaga cgaaaggGCC tcgtgatacG  
 4101 cctattttta taggttaatG tcatgataat aatggtttct tagacgtcag  
 4151 gtggcacttC tcggggaaat gtgcgcggaa cccctatttG tttattttc  
 4201 taaatacatt caaatatgtA tccgctcatG agacaataac cctgataaaat  
 4251 gcttcaataa tattggaaaaa ggaagagatG gagtattCAA catttccgtG  
 4301 tcGCCCTtat tcccttttG gcggcatttG gcCcCtCtG tttgctcac  
 4351 ccagaaACGc tggtaaaatG aaaagatGt gaagatCAGt tgggtgcacG  
 4401 agtgggttac atcgaactGg atctcaacAG cggtaagatC cttgagagtt  
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 4551 ccgcataCAC tattctcaga atgacttGgt tgagtactCA ccagtacAG  
 4601 aaaagcatct tacggatggc atgacagtAA gagaattatG cagtgtcGCC  
 4651 ataaccatGA gtgataaacC tgcggccaaC ttacttctGA caacgatcgg  
 4701 aggaccGAAG gagctaaccG ctttttGca caacatgggg gatcatgtAA  
 4751 ctcgccttGA tcgttggGA ccggagctGA atgaagccat accaaacgac  
 4801 gagcgtgaca ccacgatGCC tggtagcaatG gcaacaacGt tgCgcaaaact  
 4851 attaactGGC gaactactt ctctagCTTC ccggcaacAA ttaatagact  
 4901 ggatggaggc ggataaaAGt gcaggaccAC ttctgcgtc ggcCcTTCCG  
 4951 gctggctggT ttattgctGA taaatCTGGA gccggtgagc gtgggtctcg  
 5001 cggtatCatt gcagcactGG ggcagatGG taagCCtCC cgtatcgtag  
 5051 ttatctacac gacggggAGt caggcaactA tggatgaaAC aaatagacAG  
 5101 atcgctgaga taggtgcctC actgattaAG cattgttaAC tgcagacca  
 5151 agtttactCA tataactt agattgattt aaaacttcat ttttaatttA

FIGURE 23B

p43rmsENC-AT

Page 3

5201 aaaggatcta ggtgaagatc ctttttata atctcatgac caaaatccct  
5251 taacgtgagt ttcgttcca ctgagcgta gaccccgtag aaaagatcaa  
5301 aggatcttct tgagatcctt ttttctgcg cgtaatctgc tgcttgaaa  
5351 caaaaaaacc accgctacca gcggtggtt gtttgcggta tcaagagcta  
5401 ccaactctt ttccgaaggt aactggctc agcagagcgc agataccaa  
5451 tactgtcctt ctagtgtac cgtagttagg ccaccacttc aagaactctg  
5501 tagcacccgc tacataaccc tcctctgctaa tcctgttacc agtggctgct  
5551 gccagtggcg ataagtctgt tcttaccggg ttggactcaa gacgatagtt  
5601 accgataag ggcgcagggtt cgggctgaac ggggggttcg tgcacacagc  
5651 ccagcttgaa gcgaacgacc tacacccgaac ttagataacct acagcgtgag  
5701 cattgagaaa gcgccacgc tcccgaaggg agaaaggcgg acaggtatcc  
5751 ggtaagcggc agggtcggaa caggagagcg cacgagggag cttccagggg  
5801 gaaacgcctg gtatctttat agtcctgtcg gtttgcctt cctctgactt  
5851 gagcgtcgat ttttgtatg ctcgtcaggg gggcggagcc tatggaaaaaa  
5901 cgccagcaac gcggcccttt tacgggttctt ggccctttgc tggccctttg  
5951 ctcacatgtt ctttcctgcg ttatccccctt attctgtggta taaccgtatt  
6001 accgccttg agtgagctga taccgctcgc cgcagccgaa cgaccgagcg  
6051 cagcgagtca gtgagcgagg aagcggaaaga gcgcggaaata cgcaaacccgc  
6101 ctctccccgc gcgttggccg attcatataat gcagggctgc ag

FIGURE 23C

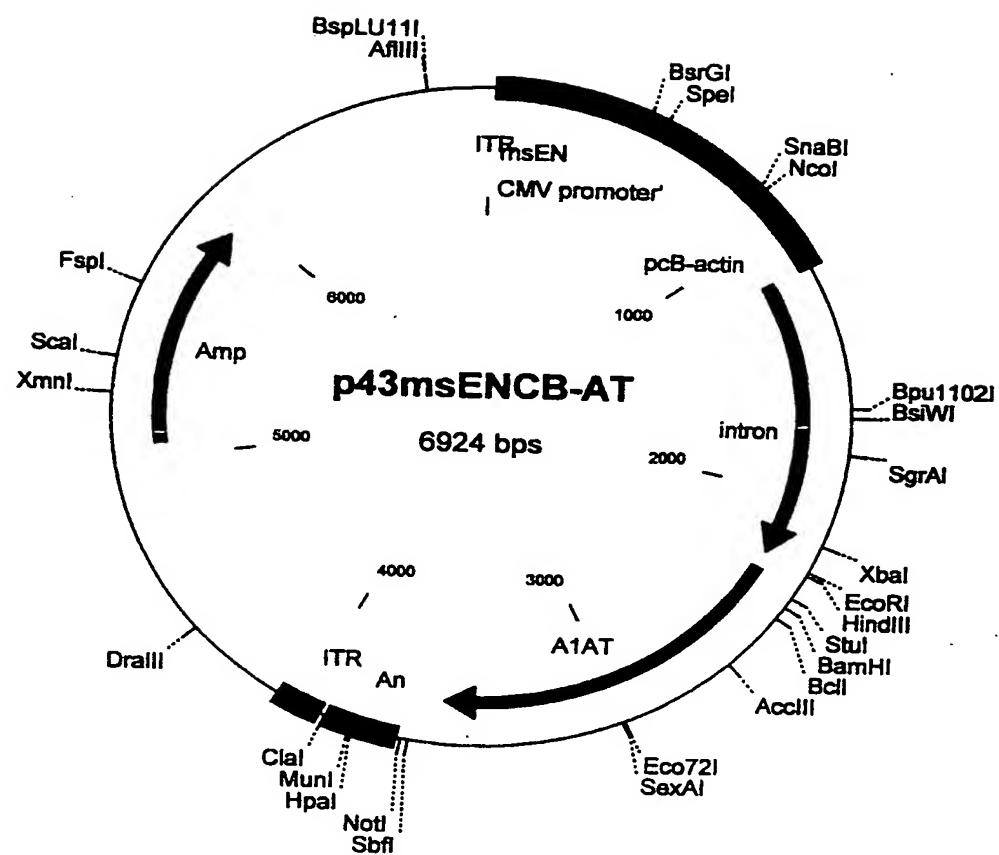


FIGURE 24

19 Apr 1999

## Sequence Data

Page 1

Molecule: p43msENCB-AT, 6924 bps DNA Circular  
Description: Ligation of msEnhacer into p43CB-AT\*  
File Name: p43msENCB-AT.cm5, dated 19 Apr 1999  
Printed: 1-6924 bps (Full), format Single Strand

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101	ggcctcagtg	agcgagcgag	cgcgcagaga	gggagtgggcc	aactccatca
151	ctaggggttc	ctagatctca	ccatcttca	cgacacccaa	atatggcgac
201	gggtgaggaa	tggtggggag	ttatTTTtag	agcggtgagg	aatgtgggc
251	aggcagcagg	tgttggcgt	ctaaaaataa	ctcccgggag	ttatTTtag
301	agcggtgagg	aatggtggac	acccaaataa	ggcgcacggca	ccattcctca
351	ccccaggcca	tatttgggtg	tcagatcttc	aatattggcc	attagccata
401	ttattcattg	gttatatagc	ataaatcaat	atggcttatt	ggccattgca
451	tacgttgtat	ctatatcata	atatgtacat	ttatattggc	tcatgtccaa
501	tatgaccgccc	atgttggcat	tgattattga	ctagttatta	atagaatca
551	attacggggt	cattagttca	tagcccatat	atggagttcc	gcgttacata
601	acttacggta	aatggcccgc	ctggctgacc	gccccaaacgac	ccccggccat
651	tgacgtcaat	aatgacgtat	gttcccatacg	taacgccaat	agggacttcc
701	cattgacgtc	aatgggtgga	gtatttacgg	taaactgccc	acttggcagt
751	acatcaagtg	tatcatatgc	caagtccgccc	ccctattgac	gtcaatgacg
801	gtaaaatggcc	cgcctggcat	tatgcccagt	acatgacctt	acgggacttt
851	cctacttggc	agtacatcta	cgtatttagtc	atcgcttatta	ccatggtcga
901	ggtgagcccc	acgttctgt	tcactctccc	catctccccc	ccctccccac
951	cccccaattt	gtatTTTATT	atTTTTAAT	tatTTTGTGc	agcgatgggg
1001	gcgggggggg	ggggggggcg	cgcgcacaggc	ggggcggggc	ggggcgaggg
1051	gcggggcggg	gcgaggcggg	gagggtgcggc	ggcagccaat	cagacggcgc
1101	cgctccgaaa	gtttcctttt	atggcgaggc	ggcggcggcgc	gcggccctat
1151	aaaaaagcgaa	gcgcgcggcg	ggcggggagtc	gctgcgacgc	tgccttcgccc
1201	ccgtgccccg	ctccgcgcgc	gcctcgcgc	gccccccccc	gctctgactg
1251	accgcgttac	tcccacaggt	gagcgggcccgg	gacggccctt	ctccctccggg
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1351	gtgaaagcct	tgagggggctc	cgggagggccc	ctttgtgcgg	gggggagcgg
1401	ctcggggggt	gcgtgcgtgt	gtgtgtgcgt	ggggagcgc	gcgtgcggcc
1451	cgcgtgcgcc	ggcggctgtg	agcgcgtgcgg	gcccggcgcgc	gggcttggc
1501	cgctccgcag	tgtgcgcgag	gggagcgcgg	ccggggggcgg	tgccccggcgg
1551	tgcggggggg	gctgcgaggg	gaacaaaggc	tgcgtgcggg	gtgtgtgcgt
1601	gggggggtga	gcaggggggtg	tgggcgcgcgc	ggtcgggctg	taaaaaaaaa
1651	ctgcacccccc	ctccccaggt	tgcgtgagcac	ggcccggtt	cgggtgcggg
1701	gctccgtacg	gggcgtggcg	cggggctcgc	cgtgccccggc	gggggggtggc
1751	ggcaggtggg	ggtgcggggc	ggggcgggggc	cgcctcgggc	cggggagggc
1801	tcggggggagg	ggcgcggcg	ccccccggagc	gcccggggct	gtcgaggcgc
1851	ggcgagccgc	agccattggc	ttttatggta	atcggtgcag	agggcgccagg
1901	gacttcttt	gtcccaaatc	tgtcgccgagc	cgaatctgg	gaggcgccgc
1951	cgcacccccc	ctagcgggcg	cggggcgaag	cgggtgcggcg	ccggcaggaa
2001	ggaaatgggc	ggggagggcc	ttcgtgcgtc	gcccgcggc	cgtcccccttc
2051	tccctctcca	gcctcggggc	tgtccggggg	gggacgggct	ccttcggggg
2101	ggacggggca	gggcgggggt	cggcttctgg	cgtgtgaccg	gcggctctag
2151	agcctctgt	aaccatgttc	atgccttctt	tttttccata	cagtcctctgg
2201	gcaacgtgt	gtttatTTTGTG	ctgtctcatac	atTTTGGCAA	agaatttcgt
2251	atcaagctt	gggattttca	ggcaccacca	ctgacactggg	acagtgaatc
2301	gacaatggcc	tcttctgtct	cgtggggcat	cctctgtctg	gcaggcctgt
2351	gctgcctgg	ccctgtctcc	ctggctgagg	atccccaggg	agatgctgcc
2401	cagaagacag	atacatccca	ccatgtatcag	gatcacccaa	ccttcaacaa

**FIGURE 24A**

p43msENCB-AT

Page 2

2451 gatcacccccc aacctggctg agttcgcctt cagcctatac cgccagctgg  
 2501 cacaccagtca caacagcacc aatatcttct tctccccagt gagcatcgct  
 2551 acaggcttgc caatgtctc cctggggacc aaggctgaca ctcacgatga  
 2601 aatcctggag ggcctgaatt tcaacctcac ggagattccg gaggctcaga  
 2651 tccatgaagg ctccaggaa ctccctccgt a cccctaacc a gccagacagc  
 2701 cagctccagc tgaccaccgg caatggctg ttccctcagcg agggctgaa  
 2751 gctagtggat aagttttgg aggatgttaa aaagtgtac cactcagaag  
 2801 ccttcactgt caacttcggg gacaccgaag aggccaagaa acagatcaac  
 2851 gattacgtgg agaagggtac tcaaggaaa attgtggatt tggtcaagga  
 2901 gcttgacaga gacacagttt ttgctctgtt gaattacatc ttctttaaag  
 2951 gcaaatggga gagaccctt gaagtcaagg acaccgagga agaggacttc  
 3001 cacgtggacc aggtgaccac cgtgaagggt cctatgtga agcgtttagg  
 3051 catgtttaac atccagcact gtaagaagct gtcagctgg gtgctgctga  
 3101 tggaaataacct gggcaatgcc accgcacatc tccctctgtc tgatgagggg  
 3151 aaactacagc acctggaaaa tgaactcacc cacgatata tcaccaagtt  
 3201 cctggaaaat gaagacagaa ggtctccag cttacattt cccaaactgt  
 3251 ccattactgg aacctatgtat ctgaagagcg tcctgggtca actggcattc  
 3301 actaaggctt tcagcaatgg ggctgaccctc tccgggtca cagaggaggg  
 3351 acccctgttcaag ctctcccaagg ccgtgcataa ggctgtgtc accatcgacg  
 3401 agaaaaggac tgaagctgtt gggccatgt ttttagaggc cataccatg  
 3451 tctatcccccc ccgagggtcaa gttcaacaaa cccttgtct tcttaatgat  
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 3801 agctgcaata aacaagttaa caacaacaat tgaccattt ttatgttca  
 3851 ggttcagggg gagatgtggg agttttttt aagcaagtt aacctctaca  
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 4001 ccgggcgtcg ggcgaccctt ggtccccgg cctcagtgtc cgagcgagcg  
 4051 cgcagagagg gagtggccaa ccccccccccc cccccccctg cagcctggcg  
 4101 taatagcgaa gaggcccgca ccgatcgccc ttcccaacag ttgcgttagcc  
 4151 tggatggcgtt atggcgccgac gcgcctgtt gcccgcatt aagcgccggcg  
 4201 ggtgtgggtt ttacgcgcag ctgcgtccgtt acacttgcac gccccttagc  
 4251 gcccgtctt ttcgccttct tcccttcctt tctcgccacg ttcgeccggct  
 4301 ttccccgtca agctctaaat cgggggtctt ctttaggggtt ccgatttagt  
 4351 gctttacggc acctcgaccc caaaaaactt gattagggtg atggttcacg  
 4401 tagtggccca tcgcctgtat agacggttt tcgcctttt acgttgaggt  
 4451 ccacgttctt taatagtttgc ctcttgcattt aaactggaa aacactcaac  
 4501 cctatctcggt tctattttt tgatttataa gggattttgc cgatttcggc  
 4551 ctattggta aaaaatgagc tgatttaaca aaaatttaac gcaattttt  
 4601 aaaaaatatt aacgtttaca atttcgtat gcccgtttt ctccttacgc  
 4651 atctgtgcgg tatttcacac cgcatatggt gcacttcgt tacaatctgc  
 4701 tctgtatgcgg catagttaa ccagccccga caccggccaa caccgcgtga  
 4751 cgcgcctgtt cgggcttgc tgctccggc atccgcttac agacaagctg  
 4801 tgaccgttcc cgggagctgc atgtgtcaga gtttttccacc gtcacccaccg  
 4851 aaacgcgcga gacgaaagggtt cctcggtata cgccttattt tataaggtaa  
 4901 tgtcatata ataatggttt cttagacgtc aggtggact tttcggggaa  
 4951 atgtgcgcgg aacccctatt tggattttt tctaaataca ttcaaataatg  
 5001 tatccgtca tgagacata accctgtata atgctcaat aatattgaaa  
 5051 aaggaagagt atgagtttccg tgcgtccctt attccctttt  
 5101 ttgcggcatt ttgccttcgtt gttttgtc acccagaaac gctgggtgaaa  
 5151 gtaaaagatg ctgaagatca gttgggtgca cgagtgggtt acatcgact

FIGURE 24B

p43msENCB-AT

Page 3

5201 ggatctcaac agcggtaaga tccttgagag ttttcgcccc gaagaacgtt  
 5251 ttccaaatgat gagcaacttt aaagtctgc tatgtggcgc ggtattatcc  
 5301 cgtattgacg ccgggcaaga gcaactcggt cgccgcatac actattctca  
 5351 gaatgactt gttgagactt caccagtac agaaaagcat cttacggatg  
 5401 gcatgacagt aagagaatta tgcaagtctg ccataaccat gagtgataac  
 5451 actgcggcca acttacttct gacaacgatc ggaggaccga aggagcta  
 5501 cgcttttttgc cacaacatgg gggatcatgt aactcgcctt gatcgttggg  
 5551 aaccggagct gaatgaagcc ataccaaacg acgagcgtga caccacgatg  
 5601 cctgttagcaa tggcaacaac gttgcgc当地 ctatataact gcaactact  
 5651 tactctagct tcccggcaac aattaataga ctggatggag gcggataaag  
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 5751 gataaaatctg gagccgggtga gcgtgggtct cgcggtatca ttgcagcact  
 5801 ggggccagat ggttaagccct cccgtatctg agttatctac acgacgggga  
 5851 gtcaggcaac tatggatgaa cgaaatagac agatcgctga gataggtgcc  
 5901 tcactgatta agcattggta actgtcagac caagttact catabataact  
 5951 ttagatttgc taaaaacttc attttaatt taaaagatc taggtgaaga  
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 6051 cactgagcgt cagacccgt agaaaagatc aaaggatctt cttagatacc  
 6101 ttttttctg cgcgtaatct gctgcttgca aaaaaaaaaa ccaccgctac  
 6151 cagcgggtgt ttgtttggcc gatcaagagc taccaactct ttttccgaag  
 6201 gtaactggct tcagcagagc gcagatacca aatactgtcc ttcttagtgc  
 6251 gccgtagttt ggcaccact tcaagaactc tgcgtctgt aatccgttta ccagtggctg  
 6301 tcgcgtctgt aatccgttta ccagtggctg ctgcgttaccg ggttggactc  
 6351 ttaccggata agacatag gtcgggctga acgggggggtt cgtgcacaca  
 6401 gcccagctt gaggcgaacga cctacaccga actgagatac ctacagctg  
 6451 cttcccgaaag ggagaaaaggc ggacaggtat agcattgaga aagcgccacg  
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 6551 atagtcctgt cgggtttcgc cacctctgac gggaaacgcc tggtatctt  
 6601 tgctcgtag gggggcggag cctatggaaa ttgagcgtcg atttttgtga  
 6651 tttacgggtc ctggccttt gctggcttt tgctcacatg ttctttcctg  
 6701 cgtttatcccc tgattctgtg gataaccgtt ttaccgcctt tgagtgagct  
 6751 gataccgtc gccgcagccg aacgaccgag cgcagcgtact cagtgagcga  
 6801 ggaagcggaa gagcgccttacgcaaaacc gcctctcccc ggcgttggc  
 6851 cgattcatta atgcaggcttgcag

FIGURE 24C

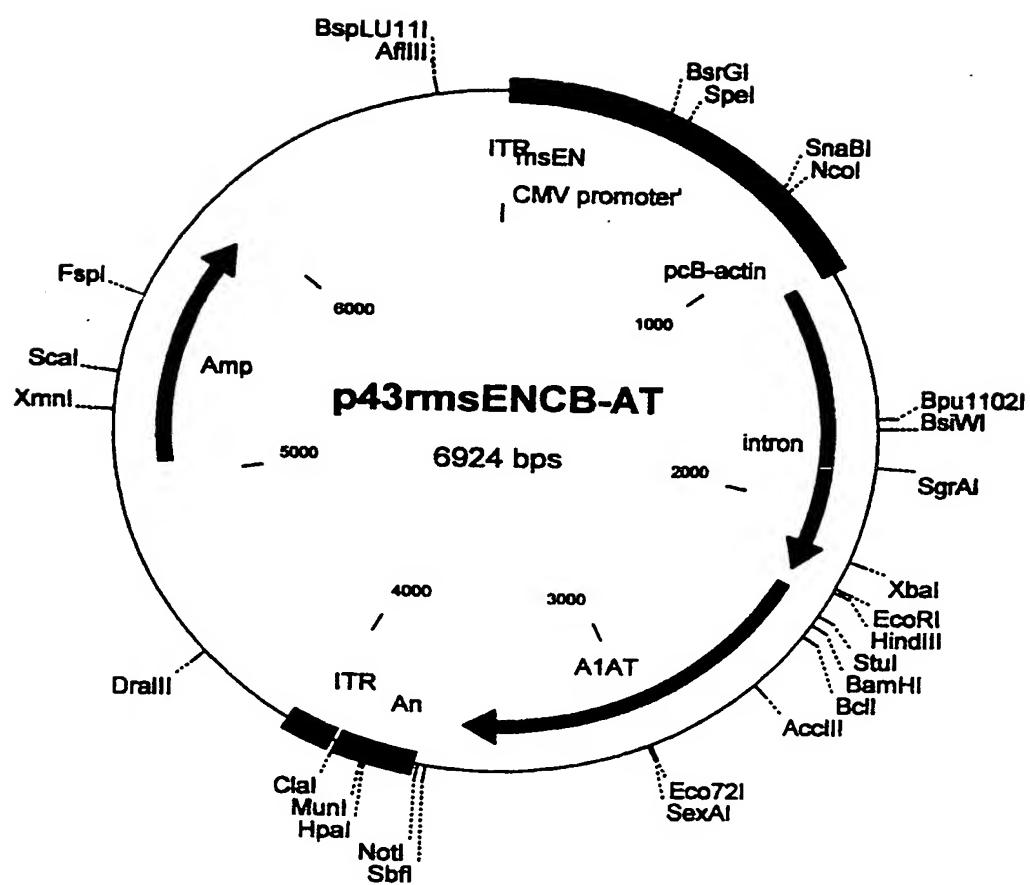


FIGURE 25

19 Apr 1999

## Sequence Data

Page 1

Molecule: p43rmsENCB-AT, 6924 bps DNA Circular  
Description: Ligation of inverted msEnhacer into p43CB-AT\*  
File Name: p43rmsCB-AT.cm5, dated 19 Apr 1999  
Printed: 1-6924 bps (Full), format Single Strand

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101	ggcctcagtg	agcgagcgag	cgcgcagaga	ggagatggcc	aactccatca
151	ctaggggtc	ctagatctga	cacccaata	tggcctgggg	tgaggaatgg
201	tgccgtcgcc	atattttgggt	gtccaccatt	cctcaccgct	ctaaaataaa
251	ctcccgggag	ttatTTTtag	agcgccaaaca	cctgtctgcct	gcccaccatt
301	cctcaccgct	ctaaaaataaa	ctccccacca	ttcctcaccc	gtcgccatat
351	ttgggtgtcg	tgaggaatgg	ttagatcttc	aatattggcc	attagccata
401	ttatttcattg	gttatatacg	ataaatcaat	attggctatt	ggccattgca
451	tacgttgtat	ctatatacata	atatgtacat	ttatattggc	tcatgtccaa
501	tatgaccgcc	atgttggcat	tgattattga	ctagttatta	atagtaatca
551	attacggggt	cattagttca	tagcccatat	atggagttcc	gcgttacata
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801	gtaaaatggcc	cgcctggcat	tatgcccagt	acatgacctt	acgggacttt
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901	ggtgagcccc	acgttctgct	tcactctccc	catctcccc	ccctcccccac
951	cccccaattt	gtattttttt	attttttaat	tattttgtgc	agcgatgggg
1001	gcgggggggg	ggggggggcg	cgcgccaggc	ggggcggggc	ggggcgaggg
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1101	cgctccgaaa	gtttcccttt	atggcgaggc	ggcgccggcg	gcggccctat
1151	aaaaagcgaa	gcgcgcggcg	ggcgggagtc	gctgcgacgc	tgccctcgcc
1201	ccgtggcccg	ctccgcggcc	gcctcgcgccc	gcccggcccg	gtcttgactg
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1301	ctgttaattag	cgcttgggtt	aatgacggct	tgtttctttt	ctgtggctgc
1351	gtgaaaagcct	tgaggggctc	cgggaggggccc	cttgtgcgg	gggggagcgg
1401	ctcggggggt	gcgtgcgtgt	gtgtgtgcgt	ggggagcgc	gcgtggggcg
1451	cgcgctgccc	ggcggctgtg	agcgctgcgg	gcmcggcg	gggctttgtg
1501	cgctccgcag	tgtgcgcgag	gggagcgcgg	ccggggggcg	tgcccccg
1551	tgccggggggg	gctgcgaggg	aaacaaaggc	tgctgcggg	gtgtgtgcgt
1601	gggggggtga	gcaggggggtg	tgggcgcggc	ggtcgggctg	taacccccc
1651	ctgcacccccc	ctcccccggagt	tgtcgagcac	ggcccggttt	cggggtgcggg
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1801	tcggggggagg	ggcgcggcg	cccccgagc	gcccggcg	gtcgaggcgc
1851	ggcgagccg	agccattggc	tttatggta	atcgtcgag	agggcgcagg
1901	gacttcctt	gtcccaaatac	tgtgcggagc	cgaaatctgg	gaggcgcgc
1951	cgcacccct	ctagcggcg	cggggcgaag	cggtgccgc	ccggcaggaa
2001	ggaaatgggc	ggggagggcc	ttcgtgcgtc	gccgcgcgc	cgtcccttc
2051	tccctctcca	gcctcggggc	tgtcccggg	gggacggctg	ccttcggggg
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2201	gcaacgtgt	gttatttgt	ctgtctcattc	attttggcaa	agaatctcgat
2251	atcaagctt	gggattttca	ggcaccacca	ctgacctggg	acagtaatc
2301	gacaatgccc	tcttctgtct	cgtggggcat	cctcctgctg	gcaggcctgt
2351	gctgccttgt	ccctgtctcc	ctggctgagg	atccccaggg	agatgctgcc
2401	cagaagacag	atacatccca	ccatgatcaq	qatcacccaa	ccttcaaccaa

**FIGURE 25A**

p43rmsENCB-AT

Page 2

2451 gatcaccccc aacctggctg agttcgccctt cagcctatac cgccagctgg  
 2501 cacaccagtc caacagcacc aatatcttct tctcccccagt gaggcatcgct  
 2551 acagcctttg caatgctc cctggggacc aaggctgaca ctcacgatga  
 2601 aatcctggag ggcctgaatt tcaacctcac ggagattccg gaggctcaga  
 2651 tccatgaagg cttccagggaa ctccctccgtt ccctcaacca gccagacagc  
 2701 cagctccagc tgaccacccgg caatggcctg ttccctcagcg agggcctgaa  
 2751 gcttagtgat aagttttgg aggatgttaa aaagttgtac cactcagaag  
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 2851 gattacgtgg agaagggtac tcaaggaaa attgtggatt tggtaagga  
 2901 gcttgacaga gacacagtt ttgtctctggt gaattacatc ttctttaaag  
 2951 gcaaatggga gagaccctt gaagtcaagg acaccggaa agaggacttc  
 3001 cacgtggacc aggtgaccac cgtgaaggtg cctatgtga agcgtttagg  
 3051 catgtttaac atccagcact gtaagaagct gtccagctgg gtgctgtga  
 3101 tgaataaccc gggcaatgcc accggcatct ttttcctgcc tgatgagggg  
 3151 aaactacagc acctggaaaaa tgaactcacc cacgatata tcaccaaagt  
 3201 cctggaaaat gaagacagaaa ggtctgccag cttacattta cccaaactgt  
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 3301 actaaggctt tcagcaatgg ggctgacctc tccgggtca cagaggagc  
 3351 acccctgaag ctctccaagg ccgtgcataa ggctgtgctg accatcgacg  
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 3801 agctgcaata aacaaggtaa caacaacaat tgcatttcatt ttatgttca  
 3851 ggttcagggg gagatgtggg aggtttttt aagcaagtaa aacctctaca  
 3901 aatgtgttaa aatcgataag gatctaggaa cccctagtga tggagttggc  
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 4001 cccggcgtcg ggcgacctt ggtcgcccg cctcgttgc cggcgcgc  
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 4751 cgcgccttga cgggcttgc tgctccggc atccgccttac agacaagctg  
 4801 tgaccgtctc cgggagctgc atgtgtcaga ggttttacc gtcatcacccg  
 4851 aaacgcgcga gacgaaaggg cctcggtata cgcctttt tataaggtaa  
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 5051 aaggaagagt atgagtattt aacatttccg tgcgcctt attccctttt  
 5101 ttgcggcatt ttgccttcctt gttttgtctt acccagaaac gctggtaaa  
 5151 gtaaaagatg ctgaagatca gttgggtgca cgagtgggtt acatcgact

FIGURE 25B

p43rmsENCB-AT

Page 3

5201 ggatctcaac agcggtaaga tcctttagag ttttcgcccc gaagaacgtt  
5251 ttccaaatgtat gaggacttt aaagtctgc tatgtggcgc ggtattatcc  
5301 cgtatttgacg ccgggcaaga gcaactcggt cgccgcatac actattctca  
5351 gaatgacttg gttgagactt caccagtac agaaaagcat cttacggatg  
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5451 actgcggcca acttacttct gacaacgatc ggaggaccga aggagcta  
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